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RecurIndex-Guided postoperative radiotherapy with or without Avoidance of Irradiation of regional Nodes in 1-3 node-positive breast cancer (RIGAIN): a study protocol for a multicenter, open-label, randomized controlled prospective phase III trial

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ABSTRACT

Introduction

Postoperative radiotherapy in breast cancer patients with 1-3 lymph node metastases, particularly within the pT1-2N1M0 cohort with a low clinical risk of local-regional recurrence (LRR), has incited a discourse surrounding personalized treatment strategies. The Recurrence Index (RI) model capably differentiates patients based on their level of LRR risk. This research aims to validate whether a more aggressive treatment approach can enhance clinical outcomes in N1 patients who possess a clinically low risk of LRR, yet a high RecurIndex-determined risk of LRR. Specifically, this entails postoperative whole breast irradiation (WBI) combined with regional lymph node irradiation (RNI) following breast-conserving surgery (BCS) or chest wall irradiation (CWI) with RNI after mastectomy.

Methods and Analysis

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. In this study, patients with low clinical LRR risk but high RecurIndex LRR risk are randomly assigned in a 1:1 ratio to the experimental group or the control group. In the experimental group, RNI is performed and the control group omits RNI. Efficacy and safety analyses will be conducted, enrolling a total of 540 patients (270 per group). The primary endpoint is invasive disease-free survival, and secondary endpoints include any first recurrence, local-regional recurrence-free survival, distant metastasis-free survival, recurrence-free survival, overall survival, disease-free survival, breast cancer-specific mortality, and assessment of patient quality of life. The study began in April 2023 and will continue for at least 10 years.

Ethics and dissemination

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2022-097-02). It adheres to the Helsinki Declaration and good clinical practice. Approval from the Chinese Human Genetic Resources Office (Reference Number: 2020SQCJ2358). **Trial registration number** NCT04069884

STRENGTHS AND LIMITATIONS OF THIS STUDY

This study represents the first international investigation into the value of a multigene model in guiding precision radiotherapy for N1 patients, particularly when clinical and genetic LRR risk assessments are discordant, specifically in cases of patients who are clinically low LRR risk but genetically high-risk.

The trial is designed as a multicenter, open-label, randomized, controlled phase III study, which will enhance the rigor of the investigation and reduce potential bias.

While the follow-up period for this study is set at 5 years, it may be necessary to extend the followup to 10 or 15 years to obtain sufficient data on long-term survival benefits.

INTRODUCTION

Patients with 1-3 axillary lymph node metastases constitute approximately 25 to 30% of early operable breast cancer cases. Radiotherapy plays a pivotal role in the comprehensive treatment of breast cancer^{1,2}. However, the benefit of postoperative radiotherapy for N1 breast cancer patients, particularly in terms of survival improvement, remains a topic of substantial debate. Studies conducted in the 1990s such as the Vancouver study, DBCG-82b/82c, and the early meta-analysis by EBCTCG (including the N1 subgroup) consistently demonstrated that postoperative radiotherapy significantly enhances disease-free survival (DFS) and overall survival (OS) for patients³⁻⁷. Consequently, N1 becomes a relative indication for postoperative radiotherapy. The 2011/2014 EBCTCG meta-analysis further suggested that postoperative radiotherapy could convert a 1.5% reduction in the 10-year any first recurrence rate (AFRR) into a 1% 20-year OS benefit^{8,9}. The MA20 and EORTC 22922 studies published in 2015^{10,11}, which focused on T1-2N1 patients, especially those with high clinical risk of LRR and compared postoperative RNI after BCS or without RNI, found that more aggressive postoperative RNI for T1-2N1 patients could result in better distant metastases-free survival (DMFS), DFS, or breast cancer-specific mortality (BCSM). The Vancouver study's 20-year long-term follow-up results demonstrated the long-term OS benefit of postoperative radiotherapy in the N1 subgroup. These milestone studies further reinforced the value and recommendation of postoperative radiotherapy for N1 breast cancer patients, rendering N1 staging a strong relative indication for postoperative radiotherapy and increasing the number of patients actively accepting postoperative radiotherapy. Nevertheless, not all N1 patients can benefit from postoperative radiotherapy. Some real-world retrospective studies reveal limited LRR and/or survival improvement from postoperative radiotherapy, particularly RNI therapy, among certain N1 patients, especially those with relatively low clinical risk. Consequently, the necessity of radiotherapy for clinically low LRR risk N1 patients remains a topic of significant controversy and uncertainty. Clinical practice often presents varying professional recommendations for postoperative radiotherapy in low-risk N1 patients, resulting in the exclusion of a substantial number of patients solely based on traditional clinical and pathological features. However, this omission of RNI could lead to inadequate treatment, with potential implications for tumor recurrence, metastasis, and patient survival. Conversely, a uniform approach of postoperative radiotherapy for all clinically low LRR risk N1 patients would inevitably result in overtreatment and expose patients to additional risks such as radiation-induced injury and related complications, thereby impacting their quality of life¹²⁻¹⁵.

When considering low-risk N1 breast cancer patients, then, the primary objective is to identify the actual high-risk patients concealed within the clinically low-risk population and to strategically administer postoperative radiotherapy. This represents one of the essential development directions of early breast cancer "precision radiotherapy" in the future. Achieving individualized and precise radiotherapy depends on the discovery of molecular genetic prediction models that can accurately predict local-regional recurrence risk in a scientific, reliable, and accessible manner. Currently approved multi-gene detection models abroad include Oncotype DX, MammaPrint, and EndoPredict. Oncotype DX is the most representative and extensively utilized multi-gene prognostic analysis method, primarily employed to guide early luminal low-risk patients to avoid adjuvant chemotherapy. Oncotype DX is currently more frequently used in the radiotherapy field to identify low-risk elderly N0 breast-conserving patients exempt from postoperative radiotherapy. Although the predictive value in the N1 population has initially demonstrated some clinical

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significance, contradictions exist between various research findings¹⁶⁻¹⁹. No prospective high-level evidence for multi-gene models predicting RNI benefits in N1 patients is currently available. The clinical trial Tailor RT (MA 39) conducted by the Canadian Cancer Trials Group primarily investigates whether low-risk recurrence patients can be spared from postoperative radiotherapy or RNI. This is currently the only prospective, randomized, controlled phase III study internationally that utilizes a multi-gene predictive model to guide precise radiotherapy for N1 patients. The future research outcomes will primarily be applied to guide the omission of postoperative radiotherapy in clinically low LRR risk and genetically low-risk N1 patients. However, the significance of postoperative radiotherapy for patients with intersecting risks, especially those with clinically low-risk but genetically high-risk profiles, remains uncertain.

RecurIndex is the only risk prediction model developed based on the Chinese population for earlystage breast cancer. Consisting of 18 core genes and 10 IHC4 reference genes, it is capable of independently predicting the risk of LRR and distant metastasis²⁰⁻²⁴. Internal validation studies in Taiwan and external validation studies conducted in Singapore, Hong Kong, and the Fourth Affiliated Hospital of Hebei Medical University in China have all provided strong evidence of RecurIndex's predictive efficacy and its value in guiding radiotherapy for N1 patients^{25,26}. Low-risk and high-risk patients identified by RI-LRR had 5-year LRR rates of 0% and 7%, respectively (P=0.0146). Compared to high-risk RI-LRR patients who did not receive postoperative radiotherapy, those who underwent postoperative radiotherapy demonstrated significantly improved rates of LRR and RFS, with percentages of 88.8% vs 74.1% (P=0.0071) and 79.4% vs 59.5% (P=0.0019), respectively. These results clearly indicate the significant benefits of postoperative radiotherapy in this patient population. To date, RecurIndex has become widely recognized and clinically implemented around the Asia-Pacific region. It has been incorporated into the "Expert Consensus on Multigene Testing for Adjuvant Therapy of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer" in China and recommended in the "Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Breast Cancer 2022" for guiding precise postoperative radiotherapy in N1 patients. However, further high-level, randomized, controlled phase III clinical trials are needed to validate its clinical applications and expand its usage in the field. The most promising and crucial area for its application lies in guiding precise radiotherapy for N1 breast cancer patients.

In summary, we have begun conducting a multicenter, prospective, randomized, controlled phase III clinical study of individualized precision radiotherapy for clinically low LRR risk breast cancer patients with N1 guided by RecurIndex. This study aims to evaluate patients' local recurrence and distant metastasis risks, primarily investigating whether active postoperative radiotherapy can further improve clinical efficacy in N1 patients with clinically low risk but high RecurIndex LRR risk. The ultimate goal of this study is to provide high-level clinical evidence and reliable multigene recurrence risk prediction models to help achieve individualized precision radiotherapy for N1 breast cancer patients.

MATERIALS AND METHODS

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. The overall research process is illustrated in Figure 1. This study aims

to screen postoperative patients with early-stage breast cancer (pT1-2N1M0) who have completed standard systemic therapy and possess eligible pathological specimens for participation. The inclusion and exclusion criteria are listed in Table 1. RecurIndex testing will be performed using postoperative paraffin-embedded tissue sections from the primary lesion. The study is divided into a randomized controlled trial and an observational study based on clinical risk and RecurIndex LRR risk. Patients with low clinical risk but high RecurIndex LRR risk will be randomly assigned in a 1:1 ratio to either the experimental group (RNI) or the control group (No RNI), while patients with low clinical risk and low RecurIndex LRR risk will be included in the observational study. This article primarily focuses on the randomized controlled trial. The study participants will receive the following treatments. Experimental group: For patients who underwent BCS, RNI will be performed in combination with whole breast irradiation (WBI) + tumor bed boost irradiation. For patients who underwent mastectomy, chest wall irradiation (CWI) will be administered in combination with RNI. Control group: RNI will be omitted. For patients who underwent BCS, only WBI + tumor bed boost irradiation will be administered. For patients who underwent mastectomy, both RNI and CWI will be omitted. A comparative effectiveness analysis will be conducted. The study commenced in April 2023 and is expected to continue for a minimum of 10 years.

Randomization Method

Stratified randomization will be used for the randomized study. For the active postoperative radiotherapy trial involving the clinically low LRR risk but high RecurIndex LRR risk population, participants will be stratified by N1 status, surgical method, and enrolling hospital, and then randomized in a 1:1 ratio into the experimental and control groups.

Randomization stratification factors are as follows:

a) N1 status: N1mic or 1-2 LN macrometastasis (including N1sln), or 3 LN macrometastasis;

- b) Surgical method: breast-conserving surgery or mastectomy; and
- c) Multicenter enrolling hospital.

A central randomization system was developed by TaiMei Medical Technology Company to facilitate the randomization process. Statistical experts responsible for randomization designed the randomization parameters in advance, allowing the system to generate a random allocation table. The main clinical trial centers conduct eligibility screening for potential participants. Once deemed eligible, the researchers at each sub-center access the server via the internet and enter the information of the enrolled patients. The system then assigns a corresponding randomization number based on the random allocation table, determining the patient's placement in the respective study group.

Participants and recruitment

Patients will be recruited by radiation oncologists from each participating research center. For each interested patient, the clinician or clinical coordinator will provide a complete and comprehensive introduction to them or their designated representative, informing the patient about their rights, the risks involved, and the potential benefits they may receive to enhance their compliance with the protocol. Prior to enrollment, patients are required to sign an informed consent form, which will be kept in the Case Report Form (CRF). Patient registration is scheduled to begin on April 1, 2023, and

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is expected to continue for 5 years (tentatively until January 2028). The final collection of data for the primary outcome measures is anticipated to be completed by December 2032.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Objectives and endpoints

This study aims to evaluate whether adjuvant radiotherapy to the regional lymph nodes after breastconserving surgery or chest wall plus regional lymph node radiotherapy after total mastectomy can further improve clinical outcomes in N1 patients with low clinical risk but high RecurIndex LRR risk.

The primary endpoint is invasive disease-free survival (IDFS). Secondary endpoints are any first recurrence (AFR), local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), recurrence-free survival (RFS), overall Survival (OS), disease-free survival (DFS), breast cancer-specific mortality (BCSM) and patient quality of life assessment. The specific definitions can be found in Table 2.

During the screening period and 3 months after the end of treatment, patients in each group fill out the quality of life questionnaire (EORTC QLQ-C30), as well as the breast cancer survival quality scale (EORTC QLQ-BS23) annually during the follow-up phase. (Supplementary 1 and 2).

RecurIndex Test

RecurIndex testing was performed using postoperative paraffin-embedded tissue sections from the primary lesion of the subjects. All sections were uniformly sent to the Jiangsu Simcere Pharmaceutical Co., Ltd., Jiangsu Simcere Diagnostics Co., Ltd. Formalin-fixed, paraffin-embedded tissue blocks should be selected that cover the largest amount of tumor cells and meet the diagnostic criteria in appearance. Tissue sections with an excess amount of normal tissue, necrotic tissue, adipose tissue, or hemorrhagic tissue should not be sent for examination. The tumor cell content in the identified sections should be >50% for the test to be performed. A total of 10 consecutive sections are needed, each with a thickness of 5 microns. The sections can remain unstained and without coverslips. There is no need to oven-dry the sections; they can be air-dried naturally.

Safety Assessment Indicators

All patients participating in the RIGAIN study are required to undergo safety assessments, including acute radiation reactions and late radiation injuries for radiotherapy patients. The evaluation criteria and handling of injuries are detailed in Supplementary 4-8. Their treatment is shown in Supplementar 9. Including acute skin reactions to radiotherapy, symptomatic radiation pneumonitis, long-term cosmetic outcomes (BCS/reconstruction patients), skin fibrosis (total mastectomy patients), ischemic heart disease, upper limb edema^{27,28}, brachial plexus injury and second primary tumor²⁹.

Radiotherapy

General consideration

The overall treatment plan for each participant is determined by the researchers at the corresponding

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sub-center based on the participant's condition. Depending on their assigned group, patients will either undergo RNI or be exempted from it. Breast-conserving patients will all receive WBI. Patients should start radiotherapy within 8 weeks after completion of adjuvant chemotherapy. The regional lymph nodes include the supraclavicular lymph nodes and infraclavicular lymph nodes (unresected levels II/III axillary lymph nodes), with or without internal mammary lymph nodes (at least from the 1st to the 3rd intercostal space). For patients with minimally positive SLN and without ALND, the inclusion criteria encompass the low/intermediate axillary lymph nodes. The planned endocrine therapy and anti-HER2 treatment can be continued during the RT process.

Patient positioning and immobilization

The patient lies on a fixed device such as a breast support, vacuum bag, or foam pad. A CT scan is performed with a thickness of 3-5 mm, from the second cervical vertebra to the second lumbar vertebra. CT positioning includes surface marking, where lead wires are placed on the surgical scar of the primary lesion in breast-conserving patients or the chest wall scar in total mastectomy patients, as well as on the scar of the axillary sentinel/clearance lymph node incision. If there is a drainage site, it should also be separately marked with a lead wire or lead point.

Volumes of interest

The clinical target volume (CTV) and organs at risk (OAR) must be delineated on all CT slices, following the contouring guidelines of the Radiation Therapy Oncology Group (RTOG) and considering the actual situation at each CT slice. Detailed descriptions of CTV and OARs can be found in Supplementary 10. The margin between the planning target volume (PTV) and CTV depends on the institutional standards of each participating center, with a recommended minimum of 5 mm. Contours should be drawn according to the RTOG guidelines, including the ipsilateral and contralateral lungs, heart, humeral heads, and spinal cord.

External beam equipment and techniques

Radiation therapy techniques that can be employed include three-dimensional conformal radiotherapy (3DCRT), forward intensity-modulated radiotherapy (F-IMRT), inward intensity-modulated radiotherapy (I-IMRT), volumetric modulated arc therapy (VMAT), and helical tomotherapy (HT). Conventional radiotherapy (using a simulator for positioning and a 2D planning system to design treatment plans with external and tangential fields) and proton therapy techniques are not allowed. Some variations in treatment planning and implementation are permitted to accommodate the participating centers in adapting to the research protocol. However, it is strongly recommended that the treatment plans for enrolled patients at each center remain consistent to avoid confusion.

Dose prescription, fractionation

The whole breast target volume, or the integrated target volume of the whole breast and low to moderate axillary region, or the chest wall target volume, and the regional lymph node target volume receive a radiation dose of 5000 cGy in 25 fractions, delivered at a rate of 200 cGy per day, five days per week. Alternatively, a hypofractionated radiotherapy scheme can be chosen, with a radiation dose of 4000-4256 cGy in 15 to 16 fractions. For breast-conserving patients, a sequential tumor bed boost is performed after completion of whole breast irradiation, as determined by

individual center investigators. It can be delivered using conventional fractionation, with a dose of 1000 cGy in 5 fractions at a rate of 200 cGy per day, or by using hypofractionation, with a dose of 798 cGy-1064 cGy in 3 to 4 fractions at a rate of 266 cGy per day. If there are high-risk factors for local recurrence, such as positive surgical margins, close margins, **or young age**, the radiation dose for the tumor bed boost may be increased to 1400-1600 cGy in 7 to 8 fractions at a rate of 200 cGy per day.

DVH constraints

It is required that at least 95% of the prescribed dose to the PTV covers 95% of the PTV. The specific dose distribution is determined by each center's policy, with a recommended level as shown in Supplementary 11. For breast-conserving patients, it is recommended to achieve a central axis dose uniformity of $\leq \pm 7\%$ for PTV_2 (whole breast or integrated target volume of whole breast and low to moderate axillary region) and PTV_1 (tumor bed), and to minimize the volume receiving $\geq 105\%$ of the prescribed dose. The constraints for organs at risk should follow the Quantitative Analysis of Normal Tissue Effects in Clinical (QUANTEC) guidelines (see Supplementary 12).

Withdrawal from research and study termination

Termination of treatment

Research treatment will be terminated if any of the following conditions occur in the patient. The following are the criteria for the withdrawal or dropout of subjects:

- 1. The subject withdraws informed consent;
- 2. Any AE causes the subject to be unable to continue participating in the study;
- 3. The subject is lost to follow-up;
- 4. The subject does not comply with the study requirements and/or the investigator's instructions;
- 5. The subject has a concomitant illness or change in the subject's condition, and the investigator believes the subject is no longer suitable for the study treatment; or
- 6. For any other reason the investigator believes the subject is not suitable for continuing in the study.
- 7. If a subject drops out or withdraws, relevant safety and efficacy evaluations should be completed as soon as possible.

Study Termination

The trial will be terminated if any of the following situations occur during the trial:

- 1. Serious safety issues arise during the trial;
- 2. There is a major error in the study protocol;
- 3. The principal investigator voluntarily stops the trial; or
- 4. The administrative authority revokes the trial.
- 5. The termination of the trial may be temporary or permanent.

If the trial is terminated, all trial records should be retained for review.

Follow-up evaluation and toxicity assessment

The registration timeline, intervention measures, and assessments are presented in Table 3below.

In the follow-up phase after radiotherapy, check-ups and assessments will be performed every six months until the occurrence of an endpoint event or the end of the study. For patients without postoperative radiotherapy, check-ups and assessments will be conducted every six months after the completion of adjuvant chemotherapy until the occurrence of an endpoint event or the end of the

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study. Effectiveness evaluations include tumor imaging examinations and assessments, brain MRI or CT, bone scans, quality of life questionnaires (EORTC QLQ-C30), and breast cancer-specific quality of life scales (EORTC QLQ-BS23). Safety evaluations include but are not limited to physical examinations, ECOG PS scores, pregnancy test checks, blood routine tests, blood biochemistry tests, adverse events, and serious adverse events. At the end of the study, participants will undergo physical examinations, performance status assessments (ECOG PS), blood routine tests, blood biochemistry tests, tumor markers, breast ultrasound/MRI, mammography, chest X-ray/CT, abdominal ultrasound/CT, and EORTC QLQ-C30 and EORTC QLQ-BS23 scoring. Evaluations of concomitant medications and adverse events are also required. The end-of-study visit window is 60 months after the last participant completes radiotherapy. For participants who are withdrawn or drop out before the end of the study, safety and effectiveness assessments will be conducted according to the requirements of end-of-study safety and effectiveness visits.

Data Management and Quality Assurance

In this study, electronic case report forms (eCRF) are used to collect data, and the EDC system designated by the principal investigator is used to complete the eCRF. Monitors verify the original data to ensure that the data entered into the eCRF by authorized trial center personnel (i.e., original data) is accurate, complete, and derived from original documents. Researchers and trial institutions must provide monitors with direct access to applicable source documents and reports for inspection and IEB/EC review. A Data Safety Committee has also been established, consisting of 5 members who are independent of the project team and have signed a research confidentiality agreement. The main tasks of the committee are to review and analyze positive results (recurrence and metastasis of subjects) and to understand the actual research results (without statistical analysis) when half of the subjects are enrolled. The committee will vote on whether it is necessary to adjust the research plan. This protocol does not include investigational drugs, and any toxicities that occur during treatment should be reported to the principal investigator and their ethics committee. In addition, the sub-centers should also report to the ethics committee of their institution. All serious adverse events and other adverse events must be recorded in the case report form.

Sample Size Estimation

This study is designed for superiority, referring to authoritative postoperative radiotherapy studies MA20¹⁰ and EROTC22922¹¹ for N1 patients, in which the 5-year IDFS in the radiotherapy group and the control group were 90.7% vs 81.9% and 87.7% vs 77.1%, respectively. In the domestic RecurIndex external validation retrospective study²¹ for N1 breast cancer patients, the 5-year IDFS in the high RI-LRR risk group was 81.1% vs 69.7% in the postoperative radiotherapy group and the control group, respectively. It is expected that the 5-year IDFS for the clinically low LRR risk and high RecurIndex LRR risk population in the experimental group and control group in this study will be 89% and 82%, respectively. The superiority margin is set to improve the primary endpoint IDFS by \geq 7% (HR=0.587) in the postoperative radiotherapy research group compared to the control group. With a one-sided significance level (α) of 0.025 and a power (1- β) of 0.8, assuming the experimental group performs better than the control group, the required sample size for each group was calculated as 216 cases per group using PASS15.0 software. The allocation ratio between the experimental and control groups was set at 1:1. Considering a 5-year enrollment period, 5-year follow-up period, and potential 20% dropout rate (mainly considering the need for further 10-year and 15-year long-term

efficacy follow-up after reaching the 5-year endpoint), each group will need 270 cases, totaling 540 cases.

Statistical analysis

Descriptive statistical analyses will be conducted based on demographic characteristics such as age, gender, height, weight, and other baseline characteristics such as medical history. The Cox proportional-hazards model will be used for analysis of the primary endpoint. The Hazards Ratio and its 95% confidence interval will be calculated, including stratification factors and other covariates. Additionally, the Cox proportional-hazards model without covariates will be used to support the analysis results of the primary endpoint. Moreover, the Kaplan-Meier (KM) method will be used to calculate the median invasive disease-free survival for the two groups (experimental group vs control group), including 95% confidence intervals. KM plots will be used to illustrate the time trends of IDFS. For the secondary endpoints, the AFR of each group will be calculated, as well as the corresponding 95% Clopper-Pearson confidence intervals. LRFS, DMFS, RFS, OS, DFS, and BCSM will be analyzed for median values using the KM method (including 95% confidence intervals). The overall changes in EORTC QLQ-C30 and EORTC QLQ-BS23 scores from baseline will be summarized. Safety analysis will be conducted by summarizing adverse events, changes in laboratory test results, changes in vital signs, and study treatment exposure. The results will be reported by treatment group. All adverse events during treatment, grade 3 or higher TEAEs, serious adverse events (SAEs), radiotherapy-related SAEs, and TEAEs leading to study termination will be summarized by organ system, preferred term, and group in terms of numbers and percentages. A p value ≤ 0.05 in a two-tailed test will be considered statistically significant. Statistical analyses will be performed using SPSS V.25.0 (Statistical Package for Social Sciences) and STATA V.14.

Ethics and dissemination

This study has obtained approval from the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2022-097-02), as well as approval from the respective participating centers' ethics committees. The study is being conducted in accordance with the Helsinki Declaration and good clinical practice. Approval from the Chinese Human Genetic Resources Office was obtained on January 6, 2021, with the reference number 2020SQCJ2358. The study was registered on ClinicalTrials.gov on July 7, 2022, with the registration number NCT04069884. The research findings will be published in peer-reviewed journals. The authors will be individuals who have made significant contributions to the study, design, and implementation.

Confidentiality and protection of participants' rights and interests

Researchers are required to explain to participants that participation in the clinical trial is voluntary, and that they have the right to withdraw from the study at any stage without affecting their medical treatment and rights. Personal information of participants will be kept confidential. Participants should be informed about the nature, purpose, potential benefits, and possible risks of the clinical trial, as well as alternative treatment options. Researchers should ensure that the rights and obligations of participants, as stipulated in the declaration, are protected. Participants should be given adequate time to consider whether to participate and to sign the informed consent form.

Discussion

The RIGAIN study is a multicenter, open-label, randomized controlled phase III clinical trial. Our objective is to precisely assess patients with clinically low LRR risk N1 breast cancer who, if identified as high-risk for LRR by the RecurIndex test, may receive enhanced clinical efficacy from active RNI after BCS or CWI with RNI after mastectomy. The aim is to accurately identify patients who would benefit from intensified radiotherapy. In addition, we have established an observational study to investigate the potential to exclude RNI for patients who are clinically low LRR risk and are identified as low risk for LRR by the RecurIndex. The primary endpoint of the study is LRR, with the aim of identifying truly low-risk patients for whom radiotherapy can be safely omitted from planned treatment regimens. Similarly, the MA39 study defines a clinically and genetically low-risk LRR N1 population (age \geq 40 years, luminal A type, Oncotype DX score <18) based on comprehensive clinical pathology, molecular subtype, and a multigene model. The anticipated results from the MA39 study could potentially guide personalized RNI decisions for patients who are found to be both clinically and genetically low risk. However, this study also has limitations. Firstly, the multi-gene models used in this study were developed to predict the risk of distant metastasis, and there may be inconsistencies between the occurrence of LRR and the risk of distant metastasis in clinical patients. Secondly, future research results are primarily intended to guide the omission of postoperative radiotherapy in clinically low-risk and genomically low-risk N1 patients. However, the significance of postoperative radiotherapy in patients with intersecting risks, particularly those who are clinically low-risk but genomically high-risk, remains unclear. Lastly, this study does not provide direct evidence for the application of Oncotype DX in guiding treatment decisions for Asian patients.

Traditionally, postoperative radiotherapy has been lauded for decreasing LRR and for helping to diminish the risk of distant metastases^{10,11}. This has lead to long-term improvements in DFS and BCSS, providing the ultimate benefit to patients. Notably, this is attributed to the radiation-induced abscopal killing effect (RIAKE), which refers to a series of immunological responses induced by local high-dose radiotherapy that culminate in the elimination of tumors distant from the irradiation site²⁷. In the context of postoperative radiotherapy for patients with regionally lymph node-positive breast cancer, the abscopal effect is most pronounced in patients classified as pN1, where the survival benefit is most conspicuous⁹. Compared to mastectomy, BCS better preserves the immune microenvironment, thereby enhancing the transformation and activation of the immune response following postoperative radiotherapy. This is the primary reason for our selection of IDFS as the main endpoint in this study.

Oncotype DX and MammaPrint assays primarily assess the overall recurrence risk and mainly guide chemotherapy and endocrine treatment^{16,18,30}. Previous studies have indicated a high concordance in predicting the risk of distant metastases between the RecurIndex and the MammaPrint and Oncotype DX assays. However, some discrepancies exist in assessing the risk of LRR. The TAILORx study indicated that the RecurIndex predictive model may identify patients at risk of locoregional recurrence more accurately than the Oncotype DX^{16,31,32}.

The RecurIndex predictive model stands out amongst various multigene prediction models in earlystage breast cancer with the following unique characteristics and advantages: 1. Unlike other models that only assess overall recurrence risk and are more biased towards the risk of distant metastases,

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RecurIndex can independently assess both the risk of locoregional recurrence and distant metastases, making it more suitable to guide precision radiotherapy; 2. RecurIndex demonstrates predictive efficacy in populations with HER2 overexpression and triple-negative breast cancer, potentially serving as a precise predictor of locoregional recurrence risk in patients with these two types of N1mic tumors, which could help guide individualized radiotherapy decisions.

The study focuses on the RecurIndex risk prediction model with the aim of guiding postoperative individualized radiotherapy for pT1-2N1M0 breast cancer patients. Particular attention is paid to the "clinically low LRR risk" but "genetically high-risk" population to explore and validate the clinical benefits of postoperative radiotherapy. The study design stands out for its clinical applicability and innovation as well as strict adherence to ethical and clinical practice standards. It effectively addresses the research gap in precise radiotherapy for N1 patients with overlapping risk profiles, both domestically and internationally. The study could potentially revolutionize the practice of postoperative radiotherapy by transitioning from a discretionary approach solely based on clinical and pathological information to an individualized optimization guided by clinical-genetic risk.

We anticipate that the RIGAIN study will generate high-quality evidence, establishing a precise risk assessment framework to guide optimized radiotherapy decisions for N1 breast cancer patients.

Acknowledgements We thank all the patients who participated in this study, and the oncologists, nurses, medical physicists, RT technicians and data managers at the participating centers.

Contributors

XH, YT and ZB designed the original protocol for the study. JC contributed to study management. JL, XH, YT and ZB drafted the manuscript.JL submitted the study. YT and ZB performed the sample size calculation and data analysis. RD and FW offer genetic testing. XH, JL, YT, JC, SH, AZ, LZ, YW, ZL, HY, XX, JC, XW-L, XL, XZ, WZ and XY participated in enrollment, treatment and follow-up of patients.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1 Research Process

Abbreviation: BCS, Breast conservative surgery; RI, Recurrence Index; RNI, Regional lymph node irradiation; WBI, Whole breast irradiation; CWI, Chest wall irradiation; RT, Radiotherapy; SLNB, Sentinel lymph node biopsy; ALND, Axillary lymph node dissection Page 17 of 39

1	
2 3	Table 1 Elizibility evitoria for the study
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8 7	1. Age ≥ 18 years; ≥ 70 years;
8	2. ECOG PS ≤ 2 (Supplementary 3);
9	3. Postoperative pathology confirms the diagnosis of invasive breast cancer;
10	4. Meets the clinical definition of low risk: (1) Axillary lymph node micrometastasis (N1mic),
11	or (2) N1 patients who meet all of the following conditions: a) Age ≥ 40 years; b)
12	Lymphovascular invasion (LVI) negative or limited to individual or small foci of LVI (excluding
14	extensive or large amounts of LVI); c) Three clinical molecular subtypes (Luminal A type,
15	Luminal B1 type, and Luminal B2 type) are allowed in this study: ER-positive (ER≥1%) and
16	HER2-negative, or ER-positive (ER \geq 1%) and HER2 overexpressing, respectively.
17	5. Postoperative pathological diagnosis of axillary lymph node status as any of the following:
19	a. Sentinel lymph node biopsy or axillary lymph node dissection with micrometastasis (N1mic).
20	b Sentinel lymph node biopsy with 1-2 lymph node macrometastasis (N1sln) c. Sentinel lymph
21	node bionsy + avillary lymph node dissection or simple avillary lymph node dissection with 1-3
22	houe oropsy + axinary tympin node dissection of simple axinary tympin node dissection with 1-5
23 24	The minute instance of the stand thread thre
25	6. The primary tumor and breast underwent breast-conserving surgery or mastectomy \pm breast
26	reconstruction (autologous/prosthetic);
27	7. A thorough systemic examination (e.g., chest X-ray, ultrasound, CT, etc.) within 3 months
28	before randomization for radiotherapy must confirm no distant metastasis;
30	8. Mammography and/or MRI within 12 months before surgery or randomization for
31	radiotherapy must confirm no contralateral breast cancer;
32	9. Postoperative completion of at least 4 cycles of adjuvant chemotherapy containing
33	anthracycline or taxane regimens;
34 35	10. Radiotherapy must be performed sequentially after the completion of all adjuvant
36	chemotherapy, starting no later than 8 weeks after the end of chemotherapy;
37	11. Patients must have sufficient postoperative paraffin tissue sections of the primary tumor for
38	RecurIndex testing:
39	12 No history of other malignant tumors, except for basal cell carcinoma of the skin; and
40 41	12. No instory of other manificant turnors, except for basar cent caremonia of the skin, and
42	The state of the state of the state of the study.
43	Exclusion criteria
44	1. Confirmed 13-4, N0, N2-3, M1 stage disease before postoperative radiotherapy enrollment;
45	2. Received any neoadjuvant treatment before surgery, including chemotherapy, endocrine
40 47	therapy, targeted therapy, or radiotherapy;
48	3. Patients who underwent mastectomy and only had sentinel lymph node biopsy;
49	4. History of contralateral breast cancer or other second primary malignant tumor (excluding
50	basal cell carcinoma of the skin and cervical carcinoma in situ);
51	5. Previous history of chest radiotherapy;
53	6. Presence of severe heart, lung, liver, kidney, hematopoietic system, or nervous system
54	diseases, or mental disorders;
55	7. Presence of scleroderma or active systemic lupus erythematosus or other autoimmune
56 57	diseases.
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Table 2. The specific definitions of the study endpoints

IDEC	
IDFS	I he time from the day the subject is randomized to the earliest occurrence of invasive
	cancer local recurrence, distant metastasis, or death, but does not include contralateral
	breast second primary cancer.
AFR	Any ipsilateral chest wall, breast, regional lymph node recurrence, or distant metastasis
	event that occurs during the follow-up period.
LRFS	The time from the day the subject is randomized to the earliest occurrence of ipsilateral
	chest wall, breast, or regional lymph node recurrence or death.
DMFS	The time from the day the subject is randomized to the earliest occurrence of distant
	metastasis or death.
RFS	The time from the day the subject is randomized to the earliest occurrence of ipsilateral
	chest wall, breast, regional lymph node recurrence, distant metastasis, or death.
OS	The time from the day the subject is randomized until the patient's death.
DFS	The time from the day the subject is randomized to the recurrence of the disease or the
	patient's death due to disease progression.
BCSM	The time from the day the subject is randomized to death from breast cancer.

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Figure 1 Research Process

Abbreviation: BCS, Breast conservative surgery; RI, Recurrence Index; RNI, Regional lymph node irradiation; WBI, Whole breast irradiation; CWI, Chest wall irradiation; RT, Radiotherapy; SLNB, Sentinel lymph node biopsy; ALND, Axillary lymph node dissection Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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Spplementary 1. Quality of Life Questionnaire EORTC QLQ-C30 (version 3)

We are interested in learning some information about you and your health status. Please answer all of the following questions independently and circle the answer that is most appropriate for you. There are no "correct" or "incorrect" answers. The information you provide will be kept strictly confidential.

Date of birth (year, month, day):	
Today's date (year, month, day):	

	No	A little	Some	Very much
1.Do you feel difficulty when you do some laborious movements, such as lifting	1	2	3	4
heavy shopping bags or luggage?				
2. Do you find it difficult to walk long distances?	1	2	3	4
3. Do you find it difficult to walk short distances outdoors?	1	2	3	4
4. During the day, do you have to lie in bed or sit in a chair?	1	2	3	4
5. Do you need assistance with eating, dressing, washing or going to the	1	2	3	4
bathroom?				
In the past week:	1	2	3	4
6. Are your work or daily activities limited by physical ability?	1	2	3	4
7. Are your hobbies and leisure activities physically limited?	1	2	3	4
8. Do you ever feel short of breath?	1	2	3	4
9. Have you ever had any pain?	1	2	3	4
10. Have you ever needed rest?	1	2	3	4
11. Have you ever felt sleep deprived?	1	2	3	4
12. Have you ever felt weak?	1	2	3	4
13. Have you ever felt a lack of appetite?	1	2	3	4
14. Have you ever felt nauseous and wanted to vomit?	1	2	3	4
15. Have you ever vomited?	1	2	3	4
16. Have you ever had constipation?	1	2	3	4
17. Have you ever had diarrhea?	1	2	3	4
18. Do you ever feel tired?	1	2	3	4
19. Does pain interfere with your daily activities?	1	2	3	4
20. Do you have difficulty concentrating on things, such as reading the	1	2	3	4
newspaper or watching TV?				
21. Do you ever feel nervous?	1	2	3	4
22. Do you ever feel worried?	1	2	3	4
23. Do you ever feel easily irritated?	1	2	3	4
24. Do you ever feel depressed?	1	2	3	4
25. Do you ever have trouble remembering things?	1	2	3	4
26. Has your medical condition or treatment process interfered with your family	1	2	3	4
life?				
27. Has your medical condition or treatment interfered with your social	1	2	3	4
activities?				
28. Has your medical condition or treatment process caused you financial	1	2	3	4
difficulties?				
For the following questions, the numbers 1-7 represent a scale from "very poor" to "	very go	ood".		
29. How would you rate your overall health in the past week?				_
1 2 3 4 5		6		7
very poor" to				very good
30. How would you rate the overall quality of your life in the past week?				-
1 2 3 4 5		6		7
very poor" to				very good
Patients sometimes have the following clinical symptoms. Please indicate the extent	of thes	se clinical s	ymptoms	or problems you
have had in the past week, circling the answer that best applies to you.			~	¥ ¥ 1
21 D 1 1 (9	NO	A little	Some	Very much
31. Do you cough a lot?	1	2	3	4
32. Do you cough up blood (blood in sputum)?	1	2	3	4
33. Do you leel short of breath when you rest?	1	2	2	4
34. Do you feel short of breath when you take a walk?	1	2	3	4
35. Do you feel short of breath when climbing stairs?	1	2	3	4
36. Have you ever had pain in your mouth or tongue?	1	2	3	4
37. Have you ever had difficulty swallowing?	1	2	3	4
38. Have you ever had tinging/numbress in your hands and feet?	1	2	3	4
39. Have you ever had hair loss?	1	2	3	4
40. Have you ever had chest pains?	1	2	3	4
41. Have you ever had pain in your arms or shoulders?	1	2	3	4
42. Have you ever had any pain in other parts of your body?	1	2	3	4
11 yes, please write down the area:				
45. nave you ever taken any painkillers?				
1. res Z.NO	1	2	2	4
II you have used it, does it help much with pain?	1	2	3	4

34 Supplementary 2. Hreast Cancer Sarvival Quality Scale FORTC 010-JR23 95 In the past 1 week In the past 1 week 10 Do your food and drinks taste different than usual? 1 2 3 4 10 Do your food and drinks taste different than usual? 1 2 3 4 10 Do your cosh unit (e) the normofitable, or tear up? 1 2 3 4 10 Do your repsh unit, (e) the normofitable, or tear up? 1 2 3 4 11 Do your food and drinks taste different than usual? 1 2 3 4 12 Do your teels its, does it bother you? 1 2 3 4 13 Do your feel less physically attractive due to illness or treatment? 1 2 3 4 14 Do your feel less physically attractive due to illness or iteratment? 1 2 3 4 14 Ib Do you have difficulty looking at your naked body? 1 2 3 4 15 How there set wow worked aboot your future health? 1 2 3 4 15 How thave set, to wowlint	2					
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ECOG scoring criteria	Scoring
Mobility is completely normal and does not differ in any way from that before the	0
onset of the disease	
Can walk freely and perform light physical activities, including general housework	1
or office work, but cannot perform heavier physical activities	•
Able to walk freely and take care of themselves, but have lost the ability to work,	2
Only partially able to take care of themselves, bedridden or wheelchair bound for	3
more than half of the day	5
Bedridden and unable to care for themselves	4
Death	5

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Supplementary 4. Evalu	nation criteria for common adverse	e events (CTCAE Version 4.	03)	078049 oi Including	
excerpt, normal commo Adverse Events	n adverse event evaluation criteria	a is grade 0)	Grading		
	1	2	3		5
Hemoglobin g/L	Normal value -10.0	10.0-8.0	8.0-6.5	<6. 5 6 20	
Leukocytes(10 ⁹ /L)	Normal value-3.0	3.0-2.0	2.0-1.0	<1.024	
Neutrophils(10 ⁹ /L)	Normal value-1.5	1.5-1.0	1.0-0.5		
Platelets(10 ⁹ /L)	Normal value-75	75-50	50-25	<25 g (25 g	
Transaminase ALT/AST	≤2.5×N	2.6-5.0×N	5. 1-20×N	>20¥#peri	
Alkaline phosphatase	$\leq 2.5 \times N$	2.6−5.0×N	5.1-20×N		
Bilirubin	ULN-1.5 \times N	1. 5−3. 0×N	3.0-10×N	>10 \$ 0	
Creatinine Cr	ULN-1.5 \times N	1.5-3.0×N	3.0-10×N		
Weight gain/loss	5.0-10%	10-20%	≥20%	s) .	
Vomiting	Vomiting 1 time in 24h during treatment	Vomiting 2-5 times in 24h during treatment	Vomiting ≥ 6 times in 24h during treatment or requiring fluids	Life-tive eatening and requires upent treatment	Death
Coughing sputum	Occasional/mild coughing of sputum	Moderate cough and sputum; interferes with instrumental daily life	Persistent heavy coughing and limited personal self- care	.bmj.co	
Pneumonia	Asymptomatic; clinical examination or diagnostic findings only; no intervention required	Symptomatic (mild cough and/or dyspnea, with or without fever); requires clinical intervention; interferes with instrumental daily life	Severe symptoms; limited personal autonomy; need for oxygen	Life-threatening respiratory-dysfunction; requiring utgent treatment (acheotomy or intugation)	Death
Acute coronary syndrome		Symptomatic, progressive angina; normal cardiac enzymes; hemodynamically stable	Symptomatic, unstable angina with/ or acute myocardial infarction, abnormal cardiac enzymatic parameters, hemodynamically stable	Symptomatic, unstable angina with or acute myocardiaginfarction, abnormal ardiac enzymatic garameters, hemodynagic instability	Death

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Left ventricular systolic insufficiency			Symptoms of decreased ejection fraction	Uncongrollable heart failure with declining ejection frætion requirage frætion interven gog	Death
Heart Failure	Asymptomatic, with abnormalities detected by laboratory tests (e.g., natriuretic peptide) or cardiac imaging	Mild to moderate symptoms with activity or exercise	Symptoms occur at rest or with light activity or exercise; requires treatment	Life-the strain of the state of	Death
Limb edema	Comparison using the greatest difference in volume or circumference, with 5% to 10% variation between limbs; edema or blurred anatomy that can only be detected on close examination	Comparison using the largest difference in volume or circumference, 10% <~30% difference between limbs; disappearance of skin folds; apparent loss of limb anatomy, change in shape; interferes with instrumental daily living	>30% volume variation between limbs; severe changes in limb shape; limited personal autonomy	ded from http://bmjopen.bmj.o perieur (ABES) . and data mining, Al training, a	
Neurotoxicity - Sensory	Mild sensory abnormalities (including paresthesia), absence of deep tendon reflexes	Moderate objective sensory deficit or sensory abnormalities (including tingling)	Severe objective sensory loss or sensory abnormalities that affect daily life	Persistent ensory loss, affecting function	Death
Neurotoxicity-motor	Self-perceived weakness with no objective findings	Moderate self-conscious weakness; no significant functional impairment	Self-perceived weakness with functional impairment	Paralyeis ne 14, 20	Death

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Supplementary 5. Scoring	g criteria for ac	ute radiation reactions (RTOG/EG	ORTC 1995)		
Organ Tissue	0	1	Grading		Δ
Skin	No change	Punctate skin erythema, alopecia, dry peeling or decreased sweating	Marked erythema, patchy wet peeling or moderate edema of the skin	desquamation or sungene edema	Skin ulcers, bleeding on necrosis
Larynx	No change	Mild to moderate hoarseness/cough without cough suppressants/mucosal edema	Persistent hoarseness but vocalization/involved otalgia, sore throat, flaky	soft speech, sore the contract of the speech sore the contract of the speech sore the speech speech solution of the speech speec	Significant dyspnea, wheezing, hemoptysis requiring tracheotomy intubation
Pharynx and esophagus	No change	Mild dysphagia requiring general analgesia or/non- narcotic analgesia/need for semi-liquid diet	Moderate dysphagia/narcotic analgesia/fluid	narcotics / fused fier and exudate, marked arytenoid and and and and and and and and and an	Complete obstruction, ulceration ulceration, perforation sinus tract
Lungs	No change	Mild symptoms, mild dry cough or exertional dyspnea, may be associated with imaging changes	Moderate symptoms, persistent cough requiring narcotic cough suppressant treatment or dyspnea with mild activity	Severe dysphagia dynamic for gastric feeding or intraver bus duids Severe cough or dynamic at rest with severe symptons, ineffective sedation or cough dynamic evidence of acute pneumonia, beque ing intermittent oxyge or bormonal therapy	Severe respiratory insufficiency requiring continuous oxygen or assisted ventilation
Heart	No change	Asymptomatic but objective evidence of ECG changes or pericardial abnormalities, no evidence of other cardiac disease	Symptoms not requiring specific treatment with ECG changes and imaging changes of congestive heart failure or pericardial disease	Congestive heart failure angina pectoris or pericare al ensease for which drug theraps is effective oo gies at	Congestive heart failur angina pectoris, pericardial disease or arrhythmias that have n responded to non-surgit treatment
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g criteria for late radiation injur	y (RTOG/EORTC 1995)		149 ol	
		Grading		1.
0		2		4
No change	Mild atrophy, hyperpigmentation, partial hair loss	Lamellar atrophy, moderate capillary dilatation, total hair loss	marked can be seen by the second seco	Ulcers
No change	Mild sclerosis (fibrosis) and loss of subcutaneous adipose tissue	Moderate fibrosis but asymptomatic, slight constriction of irradiated field <10% of the side length	Severe set of subcurst severe set of subcurst severe set of subcurst severe sev	Necrosis
No change	Asymptomatic or mildly symptomatic (dry cough), mild imaging signs	Moderate symptomatic pulmonary fibrosis or pneumonia (severe cough), hypothermia, patchy imaging	Severe same to matic pulmonatory Brosis or pneumonatory Brosis or imaging Elonges	severe respiratory insufficiency requiring continuous oxygenation or assisted ventilation
No change	Asymptomatic or mildly symptomatic; temporary T-wave inversion and ST changes; sinus tachycardia >110 beats/min at rest	Moderate exertional angina; mild pericarditis; normal heart size; persistent T-wave abnormalities and ST changes; low QRS waves	Severe a ging pectoris; pericard al effusion; constrictive pericarditis; moderat heart failure; cardiac enlargement; abnormation electrocardiogram	pericardial tamponade; severe heart failure; severe constrictive pericarditis
			n June 14, 2025 at Agence Bibliogra nilar technologies.	
	g criteria for late radiation injur 0 No change No change No change	scriteria for late radiation injury (RTOG/EORTC 1995) o t t t t t t t t t t t t t t t t t t	erteria for late radiation injury (RTOG/EORTC 1995) <u>The sector of the radiation injury (RTOG/EORTC 1995)</u> <u>The sector of the radiation injury (RTOG/EORTC 1995)</u> <u>The sector of the </u>	BMJ Open wordproved provided provide

	Double breast symmetry	Double nipple level gap	Breast shape on the affected side	Skin
Excellent, Good	Symmetries	≪2cm	No significant difference with the healthy side, normal appearance, no deformation of the breast lift due to scarring, no difference between the affected side and the healthy side in feel	Normal
General	Symmetries	2cm-3cm	The shape of the affected breast is basically normal or slightly smaller than the healthy side, and the feel of the affected side is slightly worse.	Lightene or shiny color
Bad	Obvious asymmetry	>3cm	The appearance of the affected side of the breast changes and is significantly smaller than the healthy side, and feels poorly in the hand	Thick, rubber- like, rough

Supprementary 6. Builder 5 en	
Grading	Breast Implants
I (no accessible envelope)	Breast implants feel as soft as non-operated breasts
II(Lightly hardened)	The softness of the breast is slightly worse, the implant can be touched
	but not seen
III(Heavy hardening)	Harder breasts, implants can be easily touched out or visible
	deformation of the implant
IV(severe contracture)	Breasts are hard, painful when touched, skin temperature becomes
	cold, deformation is obvious
Only Baker grade III and IV	are defined as periosteal contracture and require reoperation
Shiry Baker grade in and iv	are defined as periosteur contractare and require resperation

Supplementary 9. Radiotherapy-related adverse reactions and their treatment

1 Radiation-induced skin damage

Early skin reactions are those that occur within three months after the start of radiotherapy and are the most common complications in breast radiotherapy. Approximately 92% of patients receiving postlumpectomy radiotherapy will experience acute radiation-induced skin reactions, mostly grade 1 or 2 mild reactions, with a wet desquamation incidence rate of about 3%. Patients undergoing mastectomy will almost always experience acute radiation-induced skin reactions, mostly grade 2 reactions, with a wet desquamation incidence rate of about 10-20%.

Prevention is the main approach to managing radiation-induced skin complications. For grade 1 and 2 injuries, conservative treatment is primarily used. Patients should wear loose, cotton open-front underwear, avoid friction and pressure on the skin in the irradiation area, avoid using irritating products such as soap and shower gel, avoid bathing with hot water or showering the irradiation area, and not apply chemical ointments or adhesive tape. If the skin is red, swollen, itchy, or painful, do not scratch it or apply medication randomly. Follow the doctor's advice for medication, such as triethanolamine cream, compound vitamin B12 solution, and medical radiation protectants. Wet dermatitis can be treated with exposure therapy, keeping the area dry and avoiding secondary infections. Wet dermatitis that does not heal after more than two months may develop into skin necrosis, often requiring surgical treatment, with skin grafting for larger areas.

Late skin reactions include local hyperpigmentation, telangiectasia, atrophy, and fibrosis. For chronic radiation dermatitis with recurrent ulceration and significant worsening, surgery is often used to prevent malignant transformation.

2 Pharyngeal and esophageal reactions

Irradiation of the supraclavicular area can cause pharyngeal pain and difficulty swallowing, which are generally mild and self-limiting. Prevention methods include using new radiotherapy techniques, accurate positioning, precise delineation of the target area, rational design of radiation fields, and reducing or avoiding irradiation of organs at risk. Symptomatic support treatment is provided for severe reactions.

3 Radiation-induced lung injury

Radiation-induced lung injury includes early radiation pneumonitis occurring within 3 months after radiotherapy and late radiation-induced pulmonary fibrosis occurring after 3 months. Approximately 2/3 of patients will develop asymptomatic radiation pneumonitis, which does not require treatment. The incidence of symptomatic radiation pneumonitis is between 1% and 5%, usually occurring within 2 months after radiotherapy or within 6 months after radiotherapy. Patients have symptoms and signs of pneumonia, which can manifest as cough, sputum, or fever, and in severe cases, dyspnea and hypoxia. In particular, when imaging examinations (chest X-rays and CT scans) show inflammatory exudative changes in the lung tissue within the irradiation field, symptomatic radiation pneumonitis can be diagnosed after excluding lung metastasis and tuberculosis. Supportive treatment, including hormones, oxygen therapy, and even mechanical ventilation, can provide complete relief, but some patients may still develop pulmonary fibrosis within 6-12 months, even with treatment. Pulmonary fibrosis is a late injury caused by damage to the lung interstitium and pleura, and in severe cases, it can be life-threatening.

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There is currently no specific treatment for radiation pneumonitis, so prevention is more important than treatment. For patients undergoing whole-breast irradiation alone, it is recommended to use a dose-volume constraint of V20 < 22% for the ipsilateral lung. For those receiving irradiation of the supraclavicular lymph node region, a dose-volume constraint of V20 < 34% and V30 < 22% should be used for the ipsilateral lung to further evaluate the overall radiotherapy plan.

4 Radiation-induced heart damage

Radiation-induced heart disease (RIHD) initially manifests as acute pericarditis and later as coronary artery disease, chronic pericarditis, myocardial fibrosis, cardiomyopathy, heart valve damage, and cardiac conduction abnormalities. A 2013 New England Journal article reported that for every 1 Gy increase in the average dose to the heart, the incidence of major coronary events increased by 7.4%. Reducing the rick of RIHD is also focued on prevention. The most fundamental measure is to minimize

Reducing the risk of RIHD is also focused on prevention. The most fundamental measure is to minimize or avoid radiation exposure to the heart during radiotherapy. The Chinese Anti-Cancer Association Breast Cancer Diagnosis and Treatment Guidelines and Standards (2015 Edition) recommend that the average radiation dose to the heart should be assessed to be at least below 8 Gy. It is recommended to limit the heart's V30 to less than 10%. In addition, for high-risk populations of RIHD or those with cardiovascular

disease, drugs that have a protective effect on the cardiovascular system should be used as soon as possible. Regular cardiac ultrasound follow-ups should be conducted during the follow-up phase.

5 Upper limb edema

Edema in the affected upper limb is one of the common complications after breast cancer surgery and/or radiotherapy, and the extent of surgery is an important influencing factor. AMAROS research reported that the 1-year, 3-year, and 5-year lymphedema incidence rates for the ALND group were 28%, 23%, and 23%, respectively, significantly higher than the 15%, 14%, and 11% for the SLNB + axillary radiotherapy group. The incidence of upper limb lymphedema after axillary lymph node biopsy alone is 5%. Edema caused by radiotherapy usually occurs 1 to 2 months after the end of radiotherapy. Depending on the time of onset, upper limb edema caused by tumor recurrence in the axilla and supraclavicular region is not considered a true post-treatment complication.

The main prevention method for upper limb edema is to reduce axillary dissection, and postoperative progressive functional exercise is the key to preventing upper limb edema. When upper limb edema occurs, manual massage or compression therapy can be used.

6 Brachial plexus nerve injury

Radiation-induced brachial plexus nerve injury is a rare late complication after breast cancer radiotherapy, with an incidence rate of 1%-4%. Early symptoms include sensory and motor disorders in the affected limb and pain, often accompanied by severe nocturnal pain. Some cases may also have lymphedema, with progressively worsening functional impairment. In the late stage, this can lead to the loss of function of the entire limb, causing lifelong disability for the patient and severely affecting the patient's daily life and rest, with a significant impact on their mental health and quality of life. A preliminary diagnosis can be made based on the patient's radiotherapy history, asymptomatic intervals, and clinical features in clinical practice. However, it is necessary to rule out brachial plexus nerve injury caused by tumor metastasis or compression.

Radiation-induced brachial plexus nerve injury is irreversible, and there is currently no ideal treatment method, so prevention is crucial. It is essential to strictly follow the indications for radiotherapy in the lymphatic drainage area and pay attention to the radiotherapy range and radiation dose. For cases without severe pain, active measures should be taken to improve the blood supply of the nerves and surrounding soft tissues, and the earlier the diagnosis and treatment, the better the results. For advanced cases, treatment is aimed at relieving pain and improving quality of life.

7 Second primary tumors

Second primary tumors that can occur after breast cancer treatment include contralateral breast cancer and other malignant tumors such as lung cancer and soft tissue sarcomas. If these second primary tumors can be diagnosed and treated early, they do not affect the patient's survival. Therefore, regular follow-up of patients should be strengthened in clinical practice.

8 Rib fractures

The incidence is less than 1%. In most cases, patients have no noticeable symptoms, and fractures are discovered during bone scans or X-ray examinations. A small number of patients may experience chest wall or rib pain, which generally heals on its own without the need for special treatment.

9 Other side effects

During radiotherapy, patients may experience mild loss of appetite and fatigue. Therefore, it is important to adjust the diet reasonably, advocating for a "high protein, high vitamin, low fat" diet to maintain a balanced nutrition. Regularly review routine blood tests, and if a decrease in white blood cells is found, there is a risk of infection. In such cases, it may be necessary to temporarily pause radiotherapy and follow the doctor's advice for symptomatic supportive treatment.

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Suppler	nentary	10 Guidelines for Target Volume De	lineation	
Clinical of low-r	practice isk clini	involves the use of RNI+WBI(BCS) cally but high-risk in terms of Recur)/CWI (complete mastectomy) in p Index LR.	atients who are
1.1 Who 1.	ole Breas Purpos	st Clinical Target Volume (CTV_2) e: Applicable for patients who underg	go breast conservation surgery and	axillary lymph
2.	node di Target (encomp major f	issection. definition: The entire or majority of t passing the entire tumor bed target ra ascia, Rotter's lymph nodes in the pe ver axilla within the entire breast targ	he mammary gland on the affected nge, entire retro mammary space as ctoralis major and minor inter-space ret range that was not cleared	side, nd pectoralis ee, and the mid
3.	Target The low bounda small b	boundaries: • The upper boundary is wer boundary is the palpable/CT-visil ry is 5mm subcutaneously, or 0.3cm reasts. • The posterior boundary is 1-	the palpable/CT-visible upper edge ble lower edge of the gland. • The <i>a</i> subcutaneously or even up to the s -2mm behind the surface of the pec	of the gland. • Interior kin for thin and toralis major
	fascia (ribs/int regiona the inne lateral of dorsi m	adjacent to the retro mammary space ercostal muscles, but including Rotte il lymph nodes are metastatic. • The r er edge of the peristernal vessels. • The edge of the gland, anterior to the thor puscle	e), not leaving a fatty gap, excluding r's lymph nodes and axillary region medial boundary is next to the sterr he lateral boundary is the palpable acodorsal artery, anterior edge of the	g ns I and II if num, at least to or CT-visible ne latissimus
1.2 Turr	nor Bed a	and CTV 1		
1.	Purpos	e: Applicable for patients undergoing	breast-conserving surgery. Boost t	to the tumor bed
	is not n	nandatory and is determined by the p	olicy of each center. Boost is sugge	ested under the
	negativ	ng circumstances: positive margin, c re margin ≤ 2 mm) and young age (≤ 5	0 years)	IS with a
2.	Tumor with se	bed definition: The range of the exci	sed tumor and its surrounding tissu	e cavity, filled
3	Tumor	bed boundaries: Refer to: (1) The loc	cation of titanium clips with a sugg	vestion of
5.	placing	clips at the left, right, top, bottom, a	nd rear (2) The range of serous effe	usion, including
4.	Tumor	Bed CTV 1: Includes the mammary	gland and soft tissues 10-15mm be	evond the
	surgica	l excision of the tumor bed. It is sugg	gested to reduce this for patients un	dergoing
	segmen	tal resection to about 10mm. If there	is no gland beyond the tumor bed,	consider
	reducin	g it; for positive margins or presence	e of EIC or severe ADH, it is crucia	l to
1 2 1	approp	riately increase the range.	CTV 2	
1.3 integrates	Purpos	arget Area of the whole Breast and L	ower and Middle Axillary CI V_2	entinel lymph
1.	node bi	opsv.	, oreast conservation surgery plus s	entiner tympi
2.	Target	definition: Whole breast + axillary ly	mph nodes in zones I and II + Rott	er's lymph
	nodes b	between pectoralis major and minor n	nuscles.	
3.	Target	boundaries: Whole breast boundaries	refer to 5.2.3.1.1 Whole Breast Ta	rget; axillary
	zone I: minor:	axillary zone II: Follows the course of	of the axillary vein located naterally	or to the
	pectora	lis minor including the intermuscular	r space of pectoralis major and min	or (Rotter's
	LN).			×
Criter	ion	Axillary Zone I	Axillary Zone II	Rotter's Lymph Nodes
Super Bound	ior lary	Where the axillary vessels cross the lateral edge of the pectoralis minor muscle	Where the axillary vessels cross the medial edge of the pectoralis minor muscle	Including the cephalic side of the axillary artery and 5mm above the axillary vein
Inferio Bound	or lary	Where the pectoralis major muscle inserts into the rib	Where the axillary vessels cross the lateral edge of the pectoralis minor muscle	Inferior boundary of axillary zone II
Anter Bound	ior Iary	Anterior to the pectoralis major muscle and latissimus dorsi muscle	Anterior to the pectoralis minor muscle	Posterior to the pectoralis major muscle
Poster Bound	·ior lary	Anterior to the subscapularis muscle	Rib and intercostal muscles	Anterior to the pectoralis mino muscle
Media	l	Lateral edge of the pectoralis	Medial edge of the pectoralis	Medial edge of the pectoralis
Bound	lary	minor muscle	minor muscle	minor muscle
Latera	al	Medial aspect of the latissimus	Lateral edge of the pectoralis	Lateral edge of the pectoralis

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Boundary	dorsi muscle	minor muscle	minor muscle
1.4 Clinical Tai	get Volume for Chest Wall (C	CTV_CW)	
1. Purpo	se: Applicable to patients who	have undergone total mastector	ny \pm breast reconstruction
surger	у.		
2. Target	Definition: The surgical area	that may cause intraoperative sp	bread and carry the risk of
recurr	ence after total mastectomy.		
3. Target	Boundaries • Upper boundar	y is a clinical marker/0.5-1cm be	elow the clavicle head; •
Lower	· boundary is a clinical marke	r/below the contralateral breast f	old; • Anterior boundary is
the sk	n, excluding lead wire; • Pos	terior boundary is the intercostal	muscle of the rib; •
Media	l boundary is a clinical marke	er/at the junction of the sternum a	and ribs; • Lateral
bound	ary is a clinical marker/ at the	e anterior edge of the thoracic and	d dorsal vessels and the
latissi	nus dorsi.		
•	Note: 1 Includes all scar	rs, with the target area 2cm above	e and below the scar not
	reduced: ② Includes pos	toperative changes observed on (CT scan (granuloma and
	fibrotic changes, barb-like	muscle irritation signs).	0
1.5 Clinical Ta	get Volume for Supraclavicu	lar and Infraclavicular Lymph No	odes (CTV_LN)
1. Purpo	se: Suitable for group A patie	nts with low clinical risk and high	h RecurIndex LR risk
requir	ing regional lymph node radi	ation.	
2. Target	Definition: Includes supracla	avicular area, neck IV region, and	l infraclavicular lymph
nodes	(unsurgically treated Level II	I axillary lymph nodes).	
3. Target	Boundaries • Upper boundar	v is below the cricoid cartilage:	Lower boundary is 0.5-
lcm b	elow the clavicle head, where	the subclavian vein disappears.	and connects with the
whole	breast/chest wall target area;	• Anterior boundary is behind th	e sternocleidomastoid
muscl	e above and behind the pector	ralis major muscle below; • Poste	erior boundary is the
poster	ior edge of the anterior scaler	ne muscle above and the anterior	edge of the rib and
interco	ostal muscle below; • Medial	boundary is the internal jugular v	vein above, including the
entire	scalene muscle gap to the lev	el of the transverse cervical arter	y and vein, and the
junctio	on of the subclavian vein and	internal jugular vein below; • La	teral boundary is the
lateral	edge of the sternocleidomast	oid muscle above and the lateral	edge of the pectoralis
minor	muscle below.		
•	Note: ① Avoid the opera	ted axillary area (Level I and par	t of Level II); ②
	Includes the unsurgically t	reated axillary Level II area.	
1.6 Internal Ma	mmary Lymph Node Area (C	CTV IMN)	
1. Purpo	se: Applicable to Group A pat	tients with low clinical risk and h	igh RecurIndex LR,
requir	ing regional lymph node irrad	liation. Irradiation of the internal	mammary lymph node
region	is not obligatory and is deter	mined by the radiation oncologis	st.
2. Target	area definition: Those at risk	of internal mammary lymph noc	le metastasis may benefit
from i	nternal mammary lymph nod	e irradiation. It includes the 1st-3	ord intercostal spaces,
5mm i	n all directions from the intra	thoracic vessels, the upper bound	dary infusing into the
suprac	lavicular area, and the lower	boundary at the upper edge of th	e 4th rib.
3. Target	area boundaries: • Superior b	oorder: Infusion into the supracla	vicular area; • Inferior
border	: Upper edge of the fourth co	stal cartilage; • Anterior border:	Back of the pectoralis
major	muscle, back of the sternum;	Posterior border: Pleura or 5mm	m behind the internal
mamn	nary vessels; • Medial border:	5mm inside the internal mamma	ary vessels, including the
whole	space between the sternum a	nd vessels; • Lateral border: 5mm	n outside the internal
mamn	nary vessels, outer edge of the	e brachiocephalic vessels.	
•	Note: ① For high-risk pa	tients, the upper boundary extended	ds to the junction of the
	internal jugular vein, subc	lavian vein, brachiocephalic vein	, and internal mammary
	vein; 2 It is recommend	ed to expand at least 5mm inside	and outside the direction
	of the internal mammary v	vessels.	
1.7 Intraclavicu	lar Lymph Nodes (CTV intr	aclavicular-LN)	
1. Purpo	se: Applicable to Group A pat	tients with low clinical risk and h	igh RecurIndex LR,
requir	ing regional lymph node irrad	liation. Irradiation of the intracla	vicular lymph node area is
not ob	ligatory and is determined by	the radiation oncologist.	v 1 ··········
2. Target	area definition and boundari	es: Those at risk of intraclavicula	r lymph node metastasis
mav h	enefit from intraclavicular lv	mph node irradiation. The upper	boundary is the horizontal
level a	of the transverse cervical arter	ry, the lower boundary is the upper	er edge of the
brachi	ocephalic trunk, the medial b	oundary is the midline of the body	ly, and the lateral
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bound	ary is the inner edge of the su	ipraclavicular area.	
• Note: ① When irradiating the internal mammary lymph nodes, it should be routinely outlined; ② When there is metastasis of supraclavicular lymph nodes, it should be routinely outlined; ③ When there is extracapsular invasion of axillary Level II/III lymph nodes, it should be routinely outlined; ④ In patients with primary tumors invading the deep fascia, or the primary lesion located in the medial and upper part of the breast, consider outlining.

In patients who are clinically low-risk but exhibit a high-risk RecurIndex LR, regional nodal irradiation (RNI) is omitted, with whole breast irradiation (WBI) after breast-conserving surgery (BCS) only and no chest wall irradiation (CWI) after total mastectomy.

- 2.1 Entire Breast Target Volume (CTV_2):
 - 1. Purpose: Suitable for patients who have undergone breast conservation surgery with axillary lymph node dissection.
 - 2. Target Definition: This includes all or most of the glandular tissue of the affected breast, encompassing the entire tumor bed, the entire space posterior to the breast and the pectoral fascia, the interpectoral space (Rotter's lymph nodes), and any unswept low-mid axilla within the entire breast target volume.
 - 3. Target Borders: Superior border is the palpable/visible edge of the glandular tissue on CT. Inferior border is the palpable/visible lower edge of the glandular tissue on CT. Anterior border is 5 mm below the skin, but for small or thin breasts, it should be adjusted to 0.3 cm below the skin or even closer. Posterior border is 1-2 mm behind the pectoral fascia (adjacent to the space below the breast), with no fat gap left and no inclusion of ribs/intercostal muscles. If regional lymph nodes have metastasized, include interpectoral lymph nodes and unswept axillary regions I and II. Medial border is next to the sternum, extending at least to the inner edge of the peristernal vessels. Lateral border is the palpable or CT-visible outer edge of the glandular tissue, anterior to the dorsal thoracic artery, anterior edge of the latissimus dorsi muscle.

2.2 Tumor Bed and CTV1:

- 1. Purpose: Suitable for patients who have undergone breast-conserving surgery. Boosting of the tumor bed is not mandatory and depends on the policy of each center. Boosting of the tumor bed is recommended under the following conditions: positive surgical margins, close margins (invasive cancer or DCIS with negative margins ≤2 mm), young age (<50 years).
- 2. Tumor Bed Definition: The area where the tumor and surrounding tissue have been excised, filled with serum exudate or plastic tissue.
- 3. Tumor Bed Borders: Based on the location of the titanium clips. It is suggested that titanium clips be placed in five directions: left, right, up, down, and behind. The extent of serum exudate, taking into account any within the glandular tissue and beneath the scar.
- 4. Tumor Bed CTV_1: Includes the resected tumor bed extended by 10-15 mm into the glandular breast tissue and soft tissue. For patients undergoing segmental resection, this may be appropriately reduced, with a suggested 10 mm. If there's no glandular tissue outside the tumor bed, consider reducing it. In case of positive margins or presence of extensive intraductal component (EIC), severe atypical ductal hyperplasia (ADH), the range must be appropriately expanded.
- 2.3 Integrated Target Volume of the Entire Breast and Low-to-Mid Axillary Region (CTV_2):
 - 1. Purpose: Suitable for patients who have undergone breast conservation surgery with sentinel lymph node biopsy.
 - 2. Target Definition: The entire breast + lymph nodes in axillary regions I and II + interpectoral lymph nodes (Rotter's lymph nodes).
 - 3. Target Borders: For the entire breast, refer to Section1.1 Entire Breast Target Volume; Axillary Region I: anatomically marked by the small pectoral muscle, located on the lateral side of the muscle; Axillary Region II: follows the axillary vein, located posterior to the small pectoral muscle, and also includes the interpectoral space (Rotter's LN).

pertorur musere, una une merades die merpererar spude (Rotter B ER).						
Boundary	Axillary Region I	Axillary Region II	Rotter's Lymph Nodes			
Superior	Where axillary vessels cross the	Where axillary vessels cross	Including the cranial side of the			
Border	lateral edge of the small pectoral	the medial edge of the small	axillary artery and 5 mm above			
	muscle	pectoral muscle	the axillary vein			
Inferior	Where the large pectoral muscle	Where axillary vessels cross	Inferior border of axillary region			
Border	inserts into the rib	the lateral edge of the small	II			
		pectoral muscle				
Anterior	In front of the large pectoral and	In front of the small pectoral	Behind the large pectoral muscle			
Border	latissimus dorsi muscles	muscle				

Posterior Border	In front of the subscapularis muscle	Ribs and intercostal muscles	In front of the small pectoral muscle
Medial Border	Outer edge of the small pectoral muscle	Inner edge of the small pectoral muscle	Inner edge of the small pectoral muscle
Lateral Border	Inner surface of the latissimus dorsi muscle	Outer edge of the small pectoral muscle	Outer edge of the small pectoral muscle

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3	Supplementary 11 Dose distribution and organ endangerment limits		
4	Target Volume	Dmax	Dmin
5	Whole Breast PTV 2	≤107%	≥90%
6	Tumor Bed PTV_1	≤107%	≥90%
7	Whole Breast and Low-to-Mid Axilla Integrated Target Volume PTV 2	≤107%	≥90%
8	Chest Wall PTV_CW	≤110%	≥90%
9	Supraclavicular (±intranodal clavicular) PTV_LN	≤110%	≥90%
10	Internal Mammary PTV_IMN	≤110%	≥80%
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Supplementar	y 12.	Organ	dose/volume/in	npact data	for a	routine	split	exposures	(except	where	noted):
QUANTEC											

Organs	Volume	Type of irradiation (partial organ or specially indicated)	Observation index	Dose (Gy) or dose volume parameter	Incidence (%)	Dose volume parameter description
Spinal Cord	Partial spinal cord Thoracic medulla	3DCRT	Spinal cord lesions	Dmax=50	0.02	Includes all spinal cord cross-sections
Pharynx	pharyngeal constrictor muscle	3DCRT	Dysphagia and shortness of breath	Dmean< 50	<20	
larynx	Total larynx	3DCRT	Edema	Dmean< 44	<20	No chemotherapy,
	Total larynx	3DCRT	Edema	V50<27%	<20	based on a single study of patients without laryngeal cancer
lung	whole lung	3DCRT	Pneumonia	V20≤30%	<20	Double lung.
	whole lung	3DCRT	Pneumonia	Dmean=7	5	Slow dose
	whole lung	3DCRT	Pneumonia	Dmean=13	10	response
	whole lung	3DCRT	Pneumonia	Dmean=20	20	Without whole
	whole lung	3DCRT	Pneumonia	Dmean=24	30	irradiation
	whole lung	3DCRT	Pneumonia	Dmean=27	40	madiation
Esophagus	Whole	3DCRT	≥3 Grade	Dmean<	5-20	Contains
	Esophagus		acute esophagitis	34		various dose limiting
	Whole Esophagus	3DCRT	≥ grade 2 acute esophagitis	V35<50%	<30	factors. Seems to be related to dose volume
	Whole Esophagus	3DCRT	≥ grade 2 acute esophagitis	V50<40%	<30	
heart	Pericardium	3DCRT	pericarditis	Dmean<	<15	Based on
				26		individual
	Pericardium	3DCRT	pericarditis	V30<46%	<15	studies
	Whole heart	3DCRT	distant cardiac death	V25<46%	<1	High standards for assessing security based on predictive models
Liver	Whole Liver - GTV	3DCRT	Typical RILD	Dmean< 30-32	<5	Exclude patients with existing liver disease or liver cancer
	Whole Liver - GTV	3DCRT	Typical RILD	Dmean< 42	<50	Patients with liver disease
	Whole Liver - GTV	3DCRT	Typical RILD	Dmean< 28	<5	or hepatocellular carcinoma
	Whole	3DCRT	Typical	Dmean<	$<\!50$	

Liver - GTV		RILD	36		with a Child-
					Pugh rating of
					A, but not
					active
					hepatitis B,
					were included
					as observation
					indicators
Whole	3DCRT	Ulcer	D100<45	<7	
stomach					

QUANTEC: Quantitative Analysis of Illumination Response in Clinically Normal Tissues; 3DCRT: Three-Dimensional Conformal Radiotherapy; GTV: Gross Tumor Volume; RILD: Radioactive Liver Injury; RTOG: Radiation Therapy Oncology Group of Amer to per terien ont

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RecurIndex-Guided postoperative radiotherapy with or without Avoidance of Irradiation of regional Nodes in 1-3 node-positive breast cancer (RIGAIN): a study protocol for a multicenter, open-label, randomized controlled prospective phase III trial

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<u>RecurIndex-G</u>uided postoperative radiotherapy with or without <u>A</u>voidance of <u>I</u>rradiation of regional <u>N</u>odes in 1-3 node-positive breast cancer (RIGAIN): a study protocol for a multicenter, open-label, randomized controlled prospective phase III trial

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\geq The trial is designed as a multicenter, open -label, randomized, controlled phase III study.

- \geq Introduced a multigene model to guide precision radiotherapy.
- \triangleright This research utilizes IDFS as the primary endpoint.
- \geq The trial is conducted only in one country (China).

INTRODUCTION

Patients with 1-3 axillary lymph node metastases constitute approximately 25 to 30% of early operable breast cancer cases. Radiotherapy plays a pivotal role in the comprehensive treatment of breast cancer^{1,2}. However, the benefit of postoperative radiotherapy for N1 breast cancer patients,

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ABSTRACT

Introduction

Postoperative radiotherapy in breast cancer patients with 1-3 lymph node metastases, particularly within the pT1-2N1M0 cohort with a low clinical risk of local-regional recurrence (LRR), has incited a discourse surrounding personalized treatment strategies. Multigene testing for Recurrence Index (RI) model capably differentiates patients based on their level of LRR risk. This research aims to validate whether a more aggressive treatment approach can enhance clinical outcomes in N1 patients who possess a clinically low risk of LRR, yet a high RecurIndexdetermined risk of LRR. Specifically, this entails postoperative whole breast irradiation (WBI) combined with regional lymph node irradiation (RNI) following breast-conserving surgery (BCS) or chest wall irradiation (CWI) with RNI after mastectomy.

Methods and Analysis

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. In this study, patients with low clinical LRR risk but high RecurIndex LRR risk are randomly assigned in a 1:1 ratio to the experimental group or the control group. In the experimental group, RNI is performed and the control group omits RNI. Efficacy and safety analyses will be conducted, enrolling a total of 540 patients (270 per group). The primary endpoint is invasive disease-free survival, and secondary endpoints include any first recurrence, local-regional recurrence-free survival, distant metastasis-free survival, recurrencefree survival, overall survival, disease-free survival, breast cancer-specific mortality, and assessment of patient quality of life. The study began in April 2023 and with a follow-up period of 60 months after the last participant completes radiation therapy.

Ethics and dissemination

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2022-097-02, version 3.1). It adheres to the Helsinki Declaration and good clinical practice. Research findings will be submitted for publication in peer-reviewed journals. **Trial registration number NCT04069884**

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particularly in terms of survival improvement, remains a topic of substantial debate. Studies conducted in the 1990s such as the Vancouver study, DBCG-82b/82c, and the early meta-analysis by EBCTCG (including the N1 subgroup) consistently demonstrated that postoperative radiotherapy significantly enhances disease-free survival (DFS) and overall survival (OS) for patients³⁻⁷. Consequently, N1 becomes a relative indication for postoperative radiotherapy. The 2011/2014 EBCTCG meta-analysis further suggested that postoperative radiotherapy could convert a 1.5% reduction in the 10-year any first recurrence rate (AFRR) into a 1% 20-year OS benefit^{8,9}. The MA20 and EORTC 22922 studies published in 2015^{10,11}, which focused on T1-2N1

patients, especially those with high clinical risk of LRR and compared postoperative RNI after BCS

or without RNI, found that more aggressive postoperative RNI for T1-2N1 patients could result in better distant metastases-free survival (DMFS), DFS, or breast cancer-specific mortality (BCSM). The Vancouver study's 20-year long-term follow-up results demonstrated the long-term OS benefit of postoperative radiotherapy in the N1 subgroup. These milestone studies further reinforced the value and recommendation of postoperative radiotherapy for N1 breast cancer patients, rendering N1 staging a strong relative indication for postoperative radiotherapy and increasing the number of patients actively accepting postoperative radiotherapy. Nevertheless, not all N1 patients will benefit from postoperative radiotherapy. Some real-world retrospective studies reveal limited LRR and/or survival improvement from postoperative radiotherapy, particularly RNI therapy, among certain N1 patients, especially those with relatively low clinical risk. Consequently, the necessity of radiotherapy for clinically low LRR risk N1 patients remains a topic of significant controversy and uncertainty. Clinical practice often presents varying professional recommendations for postoperative radiotherapy in low-risk N1 patients, resulting in the exclusion of a substantial number of patients solely based on traditional clinical and pathological features. However, this omission of RNI could lead to inadequate treatment, with potential implications for tumor recurrence, metastasis, and patient survival. Conversely, a uniform approach of postoperative radiotherapy for all clinically low LRR risk N1 patients would inevitably result in overtreatment and expose patients to additional risks such as radiation-induced injury and related complications, thereby impacting their quality of life¹²⁻¹⁵.

When considering low-risk N1 breast cancer patients, then, the primary objective is to identify the actual high-risk patients concealed within the clinically low-risk population and to strategically administer postoperative radiotherapy. This represents one of the essential development directions of early breast cancer "precision radiotherapy" in the future. Achieving individualized and precise radiotherapy depends on the discovery of molecular genetic prediction models that can accurately predict local-regional recurrence risk in a scientific, reliable, and accessible manner. Currently approved multi-gene detection models abroad include Oncotype DX, MammaPrint, and EndoPredict. Oncotype DX is the most representative and extensively utilized multi-gene prognostic analysis method, primarily employed to guide early luminal low-risk patients to avoid adjuvant chemotherapy. Oncotype DX is currently more frequently used in the radiotherapy field to identify low-risk elderly N0 breast-conserving patients exempt from postoperative radiotherapy. Although the predictive value in the N1 population has initially demonstrated some clinical significance, contradictions exist between various research findings¹⁶⁻¹⁹. No prospective high-level evidence for multi-gene models predicting RNI benefits in N1 patients is currently available. The

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clinical trial Tailor RT (MA 39) conducted by the Canadian Cancer Trials Group primarily investigates whether low-risk recurrence patients can be spared from postoperative radiotherapy or RNI. This is currently the only prospective, randomized, controlled phase III study internationally that utilizes a multi-gene predictive model to guide precise radiotherapy for N1 patients. The future research outcomes will primarily be applied to guide the omission of postoperative radiotherapy in clinically low LRR risk and genetically low-risk N1 patients. However, the significance of postoperative radiotherapy for patients with intersecting risks, especially those with clinically low-risk but genetically high-risk profiles, remains uncertain.

RecurIndex is the only risk prediction model developed based on the Chinese population for earlystage breast cancer. Consisting of 18 core genes and 10 IHC4 reference genes, it is capable of independently predicting the risk of LRR and distant metastasis²⁰⁻²⁴. Internal validation studies in Taiwan and external validation studies conducted in Singapore, Hong Kong, and the Fourth Affiliated Hospital of Hebei Medical University in China have all provided strong evidence of RecurIndex's predictive efficacy and its value in guiding radiotherapy for N1 patients^{25,26}. Lowrisk and high-risk patients identified by RI-LRR had 5-year LRR rates of 0% and 7%, respectively (P=0.0146). Compared to high-risk RI-LRR patients who did not receive postoperative radiotherapy, those who underwent postoperative radiotherapy demonstrated significantly improved rates of LRR and RFS, with percentages of 88.8% vs 74.1% (P=0.0071) and 79.4% vs 59.5% (P=0.0019), respectively. These results clearly indicate the significant benefits of postoperative radiotherapy in this patient population. To date, RecurIndex has become widely recognized and clinically implemented around the Asia-Pacific region. It has been incorporated into the "Expert Consensus on Multigene Testing for Adjuvant Therapy of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer" in China and recommended in the "Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Breast Cancer 2022" for guiding precise postoperative radiotherapy in N1 patients. However, further high-level, randomized, controlled phase III clinical trials are needed to validate its clinical applications and expand its usage in the field. The most promising and crucial area for its application lies in guiding precise radiotherapy for N1 breast cancer patients.

In summary, we have begun conducting a multicenter, prospective, randomized, controlled phase III clinical study of individualized precision radiotherapy for clinically low LRR risk breast cancer patients with N1 guided by RecurIndex. This study aims to evaluate patients' local recurrence and distant metastasis risks, primarily investigating whether active postoperative radiotherapy can further improve clinical efficacy in N1 patients with clinically low risk but high RecurIndex LRR risk. The ultimate goal of this study is to provide high-level clinical evidence and reliable multigene recurrence risk prediction models to help achieve individualized precision radiotherapy for N1 breast cancer patients.

MATERIALS AND METHODS

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. The overall research process is illustrated in Figure 1. This study aims to screen postoperative patients with early-stage breast cancer (pT1-2N1M0) who have

completed standard systemic therapy and possess eligible pathological specimens for participation. The inclusion and exclusion criteria are listed in Table 1. RecurIndex testing will be performed using postoperative paraffin-embedded tissue sections from the primary lesion. The study is divided into a randomized controlled trial and an observational study based on clinical risk and RecurIndex LRR risk. Patients with low clinical risk but high RecurIndex LRR risk will be randomly assigned in a 1:1 ratio to either the experimental group (RNI) or the control group (No RNI), while patients with low clinical risk and low RecurIndex LRR risk will be included in the observational study. This article primarily focuses on the randomized controlled trial. The study participants will receive the following treatments. Experimental group: For patients who underwent BCS, RNI will be performed in combination with whole breast irradiation (WBI) + tumor bed boost irradiation. For patients who underwent mastectomy, chest wall irradiation (CWI) will be administered in combination with RNI. Control group: RNI will be omitted. For patients who underwent BCS, only WBI + tumor bed boost irradiation will be administered. For patients who underwent mastectomy, both RNI and CWI will be omitted. A comparative effectiveness analysis will be conducted. The study commenced in April 2023.

Randomization Method

Stratified randomization will be used for the randomized study. For the active postoperative radiotherapy trial involving the clinically low LRR risk but high RecurIndex LRR risk population, participants will be stratified by N1 status, surgical method, and enrolling hospital, and then randomized in a 1:1 ratio into the experimental and control groups.

Randomization stratification factors are as follows:

a) N1 status: N1mic or 1-2 LN macrometastasis (including N1sln), or 3 LN macrometastasis;

b) Surgical method: breast-conserving surgery or mastectomy; and

c) Multicenter enrolling hospital.

A central randomization system was developed by TaiMei Medical Technology Company to facilitate the randomization process. Statistical experts responsible for randomization designed the randomization parameters in advance, allowing the system to generate a random allocation table. The main clinical trial centers conduct eligibility screening for potential participants. Once deemed eligible, the researchers at each sub-center access the server via the internet and enter the information of the enrolled patients. The system then assigns a corresponding randomization number based on the random allocation table, determining the patient's placement in the respective study group.

Participants and recruitment

Patients will be recruited by radiation oncologists from each participating research center. For each interested patient, the clinician or clinical coordinator will provide a complete and comprehensive introduction to them or their designated representative, informing the patient about their rights, the risks involved, and the potential benefits they may receive to enhance their compliance with the protocol. Prior to enrollment, patients are required to sign an informed consent form, which will be kept in the Case Report Form (CRF). Patient registration is scheduled to begin on April 1, 2023, and is expected to continue for 5 years (tentatively until January 2028).

The final collection of data for the primary outcome measures is anticipated to be completed by December 2032.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Objectives and endpoints

This study aims to evaluate whether adjuvant radiotherapy to the regional lymph nodes after breast-conserving surgery or chest wall plus regional lymph node radiotherapy after total mastectomy can further improve clinical outcomes in N1 patients with low clinical risk but high RecurIndex LRR risk.

The primary endpoint is invasive disease-free survival (IDFS). Secondary endpoints are any first recurrence (AFR), local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), recurrence-free survival (RFS), overall Survival (OS), disease-free survival (DFS), breast cancer-specific mortality (BCSM) and patient quality of life assessment. The specific definitions can be found in Table 2.

During the screening period and 3 months after the end of treatment, patients in each group fill out the quality of life questionnaire (EORTC QLQ-C30), as well as the breast cancer survival quality scale (EORTC QLQ-BS23) annually during the follow-up phase. (Supplementary 1 and 2).

RecurIndex Test

RecurIndex testing was performed using postoperative paraffin-embedded tissue sections from the primary lesion of the subjects. All sections were uniformly sent to the Jiangsu Simcere Pharmaceutical Co., Ltd., Jiangsu Simcere Diagnostics Co. for free testing, Ltd. Formalin-fixed, paraffin-embedded tissue blocks should be selected that cover the largest amount of tumor cells and meet the diagnostic criteria in appearance. Tissue sections with an excess amount of normal tissue, necrotic tissue, adipose tissue, or hemorrhagic tissue should not be sent for examination. The tumor cell content in the identified sections should be >50% for the test to be performed. A total of 10 consecutive sections are needed, each with a thickness of 5 microns. The sections can remain unstained and without coverslips. There is no need to oven-dry the sections; they can be air-dried naturally.

Safety Assessment Indicators

All patients participating in the RIGAIN study are required to undergo safety assessments, including acute radiation reactions and late radiation injuries for radiotherapy patients. The evaluation criteria and handling of injuries are detailed in Supplementary 3-7. Their treatment is shown in Supplementar 8. Including acute skin reactions to radiotherapy, symptomatic radiation pneumonitis, long-term cosmetic outcomes (BCS/reconstruction patients), skin fibrosis (total mastectomy patients), ischemic heart disease, upper limb edema^{27,28}, brachial plexus injury and second primary tumor²⁹.

Radiotherapy General consideration The overall treatment plan for each participant is determined by the researchers at the corresponding sub-center based on the participant's condition. Depending on their assigned group, patients will either undergo RNI or be exempted from it. Breast-conserving patients will all receive WBI. Patients should start radiotherapy within 8 weeks after completion of adjuvant chemotherapy. The regional lymph nodes include the supraclavicular lymph nodes and infraclavicular lymph nodes (unresected levels II/III axillary lymph nodes), with or without internal mammary lymph nodes (at least from the 1st to the 3rd intercostal space). For patients with minimally positive SLN and without ALND, the inclusion criteria encompass the low/intermediate axillary lymph nodes. The planned endocrine therapy and anti-HER2 treatment can be continued during the RT process.

Patient positioning and immobilization

The patient lies on a fixed device such as a breast support, vacuum bag, or foam pad. A CT scan is performed with a thickness of 3-5 mm, from the second cervical vertebra to the second lumbar vertebra. CT positioning includes surface marking, where lead wires are placed on the surgical scar of the primary lesion in breast-conserving patients or the chest wall scar in total mastectomy patients, as well as on the scar of the axillary sentinel/clearance lymph node incision. If there is a drainage site, it should also be separately marked with a lead wire or lead point.

Volumes of interest

The clinical target volume (CTV) and organs at risk (OAR) must be delineated on all CT slices, following the contouring guidelines of the Radiation Therapy Oncology Group (RTOG) and considering the actual situation at each CT slice. Detailed descriptions of CTV and OARs can be found in Supplementary 9. The margin between the planning target volume (PTV) and CTV depends on the institutional standards of each participating center, with a recommended minimum of 5 mm. Contours should be drawn according to the RTOG guidelines, including the ipsilateral and contralateral lungs, heart, humeral heads, and spinal cord.

External beam equipment and techniques

Radiation therapy techniques that can be employed include three-dimensional conformal radiotherapy (3DCRT), forward intensity-modulated radiotherapy (F-IMRT), inward intensity-modulated radiotherapy (I-IMRT), volumetric modulated arc therapy (VMAT), and helical tomotherapy (HT). Conventional radiotherapy (using a simulator for positioning and a 2D planning system to design treatment plans with external and tangential fields) and proton therapy techniques are not allowed. Some variations in treatment planning and implementation are permitted to accommodate the participating centers in adapting to the research protocol. However, it is strongly recommended that the treatment plans for enrolled patients at each center remain consistent to avoid confusion.

Dose prescription, fractionation

The whole breast target volume, or the integrated target volume of the whole breast and low to moderate axillary region, or the chest wall target volume, and the regional lymph node target volume receive a radiation dose of 5000 cGy in 25 fractions, delivered at a rate of 200 cGy per day, five days per week. Alternatively, a hypofractionated radiotherapy scheme can be chosen,

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with a radiation dose of 4000-4256 cGy in 15 to 16 fractions. For breast-conserving patients, a sequential tumor bed boost is performed after completion of whole breast irradiation, as determined by individual center investigators. It can be delivered using conventional fractionation, with a dose of 1000 cGy in 5 fractions at a rate of 200 cGy per day, or by using hypofractionation, with a dose of 798 cGy-1064 cGy in 3 to 4 fractions at a rate of 266 cGy per day. If there are high-risk factors for local recurrence, such as positive surgical margins, close margins, or young age, the radiation dose for the tumor bed boost may be increased to 1400-1600 cGy in 7 to 8 fractions at a rate of 200 cGy per day.

DVH constraints

It is required that at least 95% of the prescribed dose to the PTV covers 95% of the PTV. The specific dose distribution is determined by each center's policy, with a recommended level as shown in Supplementary 10. For breast-conserving patients, it is recommended to achieve a central axis dose uniformity of $\leq \pm 7\%$ for PTV_2 (whole breast or integrated target volume of whole breast and low to moderate axillary region) and PTV_1 (tumor bed), and to minimize the volume receiving $\geq 105\%$ of the prescribed dose. The constraints for organs at risk should follow the Quantitative Analysis of Normal Tissue Effects in Clinical (QUANTEC) guidelines (see Supplementary 11).

Withdrawal from research and study termination Termination of treatment

Research treatment will be terminated if any of the following conditions occur in the patient. The following are the criteria for the withdrawal or dropout of subjects:

- 1. The subject withdraws informed consent;
- 2. Any AE causes the subject to be unable to continue participating in the study;
- 3. The subject is lost to follow-up;
- 4. The subject does not comply with the study requirements and/or the investigator's instructions;
- 5. The subject has a concomitant illness or change in the subject's condition, and the investigator believes the subject is no longer suitable for the study treatment; or
- 6. For any other reason the investigator believes the subject is not suitable for continuing in the study.
- 7. If a subject drops out or withdraws, relevant safety and efficacy evaluations should be completed as soon as possible.

Study Termination

The trial will be terminated if any of the following situations occur during the trial:

- 1. Serious safety issues arise during the trial;
- 2. There is a major error in the study protocol;
- 3. The principal investigator voluntarily stops the trial; or
- 4. The administrative authority revokes the trial.
- 5. The termination of the trial may be temporary or permanent.

If the trial is terminated, all trial records should be retained for review.

Follow-up evaluation and toxicity assessment

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The registration timeline, intervention measures, and assessments are presented in Supplementary 12. In the follow-up phase after radiotherapy, check-ups and assessments will be performed every six months until the occurrence of an endpoint event or the end of the study. For patients without postoperative radiotherapy, check-ups and assessments will be conducted every six months after the completion of adjuvant chemotherapy until the occurrence of an endpoint event or the end of the study. Effectiveness evaluations include tumor imaging examinations and assessments, brain MRI or CT, bone scans, quality of life questionnaires (EORTC OLO-C30), and breast cancerspecific quality of life scales (EORTC QLQ-BS23). Safety evaluations include but are not limited to physical examinations, ECOG PS scores, pregnancy test checks, blood routine tests, blood biochemistry tests, adverse events, and serious adverse events. At the end of the study, participants will undergo physical examinations, performance status assessments (ECOG PS), blood routine tests, blood biochemistry tests, tumor markers, breast ultrasound/MRI, mammography, chest Xray/CT, abdominal ultrasound/CT, and EORTC QLQ-C30 and EORTC QLQ-BS23 scoring. Evaluations of concomitant medications and adverse events are also required. The end-of-study visit window is 60 months after the last participant completes radiotherapy. For participants who are withdrawn or drop out before the end of the study, safety and effectiveness assessments will be conducted according to the requirements of end-of-study safety and effectiveness visits.

Data Management and Quality Assurance

In this study, electronic case report forms (eCRF) are used to collect data, and the EDC system designated by the principal investigator is used to complete the eCRF. Monitors verify the original data to ensure that the data entered into the eCRF by authorized trial center personnel (i.e., original data) is accurate, complete, and derived from original documents. Researchers and trial institutions must provide monitors with direct access to applicable source documents and reports for inspection and IEB/EC review. A Data Safety Committee has also been established, consisting of 5 members who are independent of the project team and have signed a research confidentiality agreement. The main tasks of the committee are to review and analyze positive results (recurrence and metastasis of subjects) and to understand the actual research results (without statistical analysis) when half of the subjects are enrolled. The committee will vote on whether it is necessary to adjust the research plan. This protocol does not include investigator and their ethics committee. In addition, the sub-centers should also report to the ethics committee of their institution. All serious adverse events and other adverse events must be recorded in the case report form.

Sample Size Estimation

This study is designed for superiority, referring to authoritative postoperative radiotherapy studies MA20¹⁰ and EROTC22922¹¹ for N1 patients, in which the 5-year IDFS in the radiotherapy group and the control group were 90.7% vs 81.9% and 87.7% vs 77.1%, respectively. In the domestic RecurIndex external validation retrospective study²¹ for N1 breast cancer patients, the 5-year IDFS in the high RI-LRR risk group was 81.1% vs 69.7% in the postoperative radiotherapy group and the control group, respectively. It is expected that the 5-year IDFS for the clinically low LRR risk and high RecurIndex LRR risk population in the experimental group and control group in this study will be 89% and 82%, respectively. The superiority margin is set to improve the primary

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endpoint IDFS by \geq 7% (HR=0.587) in the postoperative radiotherapy research group compared to the control group. With a one-sided significance level (α) of 0.025 and a power (1- β) of 0.8, assuming the experimental group performs better than the control group, the required sample size for each group was calculated as 216 cases per group using PASS15.0 software. The allocation ratio between the experimental and control groups was set at 1:1. Considering a 5-year enrollment period, 5-year follow-up period, and potential 20% dropout rate (mainly considering the need for further 10-year and 15-year long-term efficacy follow-up after reaching the 5-year endpoint), each group will need 270 cases, totaling 540 cases.

Statistical analysis

Descriptive statistical analyses will be conducted based on demographic characteristics such as age, gender, height, weight, and other baseline characteristics such as medical history. The Cox proportional-hazards model will be used for analysis of the primary endpoint. The Hazards Ratio and its 95% confidence interval will be calculated, including stratification factors and other covariates. Additionally, the Cox proportional-hazards model without covariates will be used to support the analysis results of the primary endpoint. Moreover, the Kaplan-Meier (KM) method will be used to calculate the median invasive disease-free survival for the two groups (experimental group vs control group), including 95% confidence intervals. KM plots will be used to illustrate the time trends of IDFS. For the secondary endpoints, the AFR of each group will be calculated, as well as the corresponding 95% Clopper-Pearson confidence intervals. LRFS, DMFS, RFS, OS, DFS, and BCSM will be analyzed for median values using the KM method (including 95% confidence intervals). The overall changes in EORTC QLQ-C30 and EORTC OLO-BS23 scores from baseline will be summarized. Safety analysis will be conducted by summarizing adverse events, changes in laboratory test results, changes in vital signs, and study treatment exposure. The results will be reported by treatment group. All adverse events during treatment, grade 3 or higher TEAEs, serious adverse events (SAEs), radiotherapy-related SAEs, and TEAEs leading to study termination will be summarized by organ system, preferred term, and group in terms of numbers and percentages. A p value ≤0.05 in a two-tailed test will be considered statistically significant. Statistical analyses will be performed using SPSS V.25.0 (Statistical Package for Social Sciences) and STATA V.14.

Ethics and dissemination

This study has obtained approval from the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2022-097-02, version 3.1), as well as approval from the respective participating centers' ethics committees. The study is being conducted in accordance with the Helsinki Declaration and good clinical practice. Approval from the Chinese Human Genetic Resources Office was obtained on January 6, 2021, with the reference number 2020SQCJ2358. The study was registered on ClinicalTrials.gov on July 7, 2022, with the registration number NCT04069884. The research findings will be published in peer-reviewed journals. The authors will be individuals who have made significant contributions to the study, design, and implementation. Any modifications to the study protocol and informed consent documents must be reviewed and approved by the Ethics Committee before implementation.

Confidentiality and protection of participants' rights and interests

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Researchers are required to explain to participants that participation in the clinical trial is voluntary, and that they have the right to withdraw from the study at any stage without affecting their medical treatment and rights. Personal information of participants will be kept confidential. Participants should be informed about the nature, purpose, potential benefits, and possible risks of the clinical trial, as well as alternative treatment options. Researchers should ensure that the rights and obligations of participants, as stipulated in the declaration, are protected. Participants should be given adequate time to consider whether to participate and to sign the informed consent form.

Discussion

The RIGAIN study is a multicenter, open-label, randomized controlled phase III clinical trial. Our objective is to precisely assess patients with clinically low LRR risk N1 breast cancer who, if identified as high-risk for LRR by the RecurIndex test, may receive enhanced clinical efficacy from active RNI after BCS or CWI with RNI after mastectomy. The aim is to accurately identify patients who would benefit from intensified radiotherapy. In addition, we have established an observational study to investigate the potential to exclude RNI for patients who are clinically low LRR risk and are identified as low risk for LRR by the RecurIndex. The primary endpoint of the study is LRR, with the aim of identifying truly low-risk patients for whom radiotherapy can be safely omitted from planned treatment regimens. Similarly, the MA39 study defines a clinically and genetically low-risk LRR N1 population (age \geq 40 years, luminal A type, Oncotype DX score <18) based on comprehensive clinical pathology, molecular subtype, and a multigene model. The anticipated results from the MA39 study could potentially guide personalized RNI decisions for patients who are found to be both clinically and genetically low risk. However, this study also has limitations. Firstly, the multi-gene models used in this study were developed to predict the risk of distant metastasis, and there may be inconsistencies between the occurrence of LRR and the risk of distant metastasis in clinical patients. Secondly, future research results are primarily intended to guide the omission of postoperative radiotherapy in clinically low-risk and genomically low-risk N1 patients. However, the significance of postoperative radiotherapy in patients with intersecting risks, particularly those who are clinically low-risk but genomically high-risk, remains unclear. Lastly, this study does not provide direct evidence for the application of Oncotype DX in guiding treatment decisions for Asian patients.

Traditionally, postoperative radiotherapy has been lauded for decreasing LRR and for helping to diminish the risk of distant metastases^{10,11}. This has lead to long-term improvements in DFS and BCSS, providing the ultimate benefit to patients. Notably, this is partly attributed to the prevention of reseeding from recurrences. Another part is attributed to the radiation-induced abscopal killing effect (RIAKE), which refers to a series of immunological responses induced by local high-dose radiotherapy that culminate in the elimination of tumors distant from the irradiation site²⁷. In the context of postoperative radiotherapy for patients with regionally lymph node-positive breast cancer, the abscopal effect is most pronounced in patients classified as pN1, where the survival benefit is most conspicuous⁹. Compared to mastectomy, BCS better preserves the immune microenvironment, thereby enhancing the transformation and activation of the immune response following postoperative radiotherapy. This is the primary reason for our selection of IDFS as the main endpoint in this study.

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Oncotype DX and MammaPrint assays primarily assess the overall recurrence risk and mainly guide chemotherapy and endocrine treatment^{16,18,30}. Previous studies have indicated a high concordance in predicting the risk of distant metastases between the RecurIndex and the MammaPrint and Oncotype DX assays. However, some discrepancies exist in assessing the risk of LRR. The TAILORx study indicated that the RecurIndex predictive model may identify patients at risk of locoregional recurrence more accurately than the Oncotype DX^{16,31,32}.

The RecurIndex predictive model stands out amongst various multigene prediction models in early-stage breast cancer with the following unique characteristics and advantages: 1. Unlike other models that only assess overall recurrence risk and are more biased towards the risk of distant metastases, RecurIndex can independently assess both the risk of locoregional recurrence and distant metastases, making it more suitable to guide precision radiotherapy; 2. RecurIndex demonstrates predictive efficacy in populations with HER2 overexpression and triple-negative breast cancer, potentially serving as a precise predictor of locoregional recurrence risk in patients with these two types of N1mic tumors, which could help guide individualized radiotherapy decisions.

The study focuses on the RecurIndex risk prediction model with the aim of guiding postoperative individualized radiotherapy for pT1-2N1M0 breast cancer patients. Particular attention is paid to the "clinically low LRR risk" but "genetically high-risk" population to explore and validate the clinical benefits of postoperative radiotherapy. The study design stands out for its clinical applicability and innovation as well as strict adherence to ethical and clinical practice standards. It effectively addresses the research gap in precise radiotherapy for N1 patients with overlapping risk profiles, both domestically and internationally. The study could potentially revolutionize the practice of postoperative radiotherapy by transitioning from a discretionary approach solely based on clinical and pathological information to an individualized optimization guided by clinical-genetic risk.

We anticipate that the RIGAIN study will generate high-quality evidence, establishing a precise risk assessment framework to guide optimized radiotherapy decisions for N1 breast cancer patients.

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Contributors

XH, YT and ZB designed the original protocol for the study. JC contributed to study management. JL, XH, YT and ZB drafted the manuscript. JL submitted the study. YT and ZB performed the sample size calculation and data analysis. RD and FW offer genetic testing. XH, JL, YT, JC, SH, AZ, LZ, YW, ZL, HY, XX, JC, XW-L, XL, XZ, WZ and XY participated in enrollment, treatment and follow-up of patients.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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Inc	usion criteria
1.	Age ≥ 18 years, ≤ 70 years;
2.	ECOG PS ≤ 2 (Supplementary 13);
3.	Postoperative pathology confirms the diagnosis of invasive breast cancer;
4.	Meets the clinical definition of low risk: (1) Axillary lymph node micrometas
(N1	mic), or $\textcircled{2}$ N1 patients who meet all of the following conditions: a) Age \ge 40 year
Lyn	nphovascular invasion (LVI) negative or limited to individual or small foci of
(exc	cluding extensive or large amounts of LVI); c) Three clinical molecular subtypes (Lu
A t	ype, Luminal B1 type, and Luminal B2 type) are allowed in this study: ER-pos
(ER	$\geq 1\%$) and HER2-negative, or ER-positive (ER $\geq 1\%$) and HER2 overexpres
resp	ectively.
5.	Postoperative pathological diagnosis of axillary lymph node status as any of the follow
a. S	entinel lymph node biopsy or axillary lymph node dissection with micrometastasis (N1
b. S	Sentinel lymph node biopsy with 1-2 lymph node macrometastasis (N1sln), c. Ser
lym	ph node biopsy + axillary lymph node dissection or simple axillary lymph node disse
with	1-3 lymph node metastasis (N1);
6.	The primary tumor and breast underwent breast-conserving surgery or mastecton
brea	ist reconstruction (autologous/prosthetic);
7.	A thorough systemic examination (e.g., chest X-ray, ultrasound, CT, etc.) within 3 mo
beto	bre randomization for radiotherapy must confirm no distant metastasis;
8.	Mammography and/or MRI within 12 months before surgery or randomization
radi	otherapy must confirm no contralateral breast cancer;
9.	Postoperative completion of at least 4 cycles of adjuvant chemotherapy contained and the sector
antr	Radiotherany must be performed acquantially after the completion of all adju
10.	reaction of a sequencially after the and of abomethorany.
11	Patients must have sufficient nestonarative paraffin tissue sections of the primary to
for	Patients must have sufficient postoperative patatini tissue sections of the primary to Recurindex testing:
12	No history of other malignant tumors, except for basal cell carcinoma of the skin: and
12.	Signed informed consent before the start of the study
Exc	lusion criteria
1	Confirmed T3-4 N0 N2-3 M1 stage disease before postoperative radiothe
enro	llment.
2.	Received any neoadiuvant treatment before surgery including chemotherapy, endo
ther	apy, targeted therapy, or radiotherapy:
3.	Patients who underwent mastectomy and only had sentinel lymph node biopsy:
4.	History of contralateral breast cancer or other second primary malignant tumor (exclu
basa	al cell carcinoma of the skin and cervical carcinoma in situ);
5.	Previous history of chest radiotherapy;
6.	Presence of severe heart, lung, liver, kidney, hematopoietic system, or nervous sy
dise	ases, or mental disorders;
7.	Presence of scleroderma or active systemic lupus erythematosus or other autoimm
dise	ases;
8.	Pregnant and breastfeeding patients.

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IDFS	The time from the day the subject is randomized to the earliest occurrence of invasive
	cancer local recurrence, distant metastasis, or death, but does not include contralateral
4.555	breast second primary cancer.
AFR	Any ipsilateral chest wall, breast, regional lymph node recurrence, or distant metastasis event that occurs during the follow-up period
LRFS	The time from the day the subject is randomized to the earliest occurrence of
LIG	ipsilateral chest wall, breast, or regional lymph node recurrence or death.
DMFS	The time from the day the subject is randomized to the earliest occurrence of distant
	metastasis or death.
RFS	The time from the day the subject is randomized to the earliest occurrence of
	ipsilateral chest wall, breast, regional lymph node recurrence, distant metastasis, or
00	death.
	The time from the day the subject is randomized until the patient's death.
DFS	The time from the day the subject is randomized to the recurrence of the disease of the national's death due to disease progression
BCSM	The time from the day the subject is randomized to death from breast cancer
DCSIVI	The time from the day the subject is randomized to death from breast earlier.

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Spplementary 1. Quality of Life Questionnaire EORTC QLQ-C30 (version 3)

We are interested in learning some information about you and your health status. Please answer all of the following questions independently and circle the answer that is most appropriate for you. There are no "correct" or "incorrect" answers. The information you provide will be kept strictly confidential.

Please	fill	in	vour	last	name:

Date of birth (year, month, day):	
Today's date (year, month, day):	

	No	A little	Some	Very much
1.Do you feel difficulty when you do some laborious movements, such as lifting	1	2	3	4
eavy shopping bags or luggage?				
. Do you find it difficult to walk long distances?	1	2	3	4
. Do you find it difficult to walk short distances outdoors?	1	2	3	4
. During the day, do you have to lie in bed or sit in a chair?	1	2	3	4
. Do you need assistance with eating, dressing, washing or going to the	1	2	3	4
hathroom?				
n the past week:	1	2	3	4
. Are your work or daily activities limited by physical ability?	1	2	3	4
. Are your hobbies and leisure activities physically limited?	1	2	3	4
Do you ever feel short of breath?	1	2	3	4
Have you ever had any pain?	1	2	3	4
). Have you ever needed rest?	1	2	3	4
I. Have you ever felt sleep deprived?	1	2	3	4
2. Have you ever felt weak?	1	2	3	4
. Have you ever felt a lack of appetite?	1	2	3	4
. Have you ever felt nauseous and wanted to vomit?	1	2	3	4
. Have you ever vomited?	1	2	3	4
5. Have you ever had constipation?	1	2	3	4
. Have you ever had diarrhea?	1	2	3	4
. Do you ever feel tired?	1	2	3	4
Does pain interfere with your daily activities?	1	2	3	4
). Do you have difficulty concentrating on things, such as reading the	1	2	3	4
ewspaper or watching TV?				
1. Do you ever feel nervous?	1	2	3	4
2. Do you ever feel worried?	1	2	3	4
3. Do you ever feel easily irritated?	1	2	3	4
I. Do you ever feel depressed?	1	2	3	4
5. Do you ever have trouble remembering things?	1	2	3	4
6. Has your medical condition or treatment process interfered with your family	1	2	3	4
fe?				
7. Has your medical condition or treatment interfered with your social	1	2	3	4
ctivities?				
8. Has your medical condition or treatment process caused you financial	1	2	3	4
difficulties?				

For the following questions, the numbers 1-7 represent a scale from "very poor" to "very good".

1								
2								
3	29. How would	l you rate your over	all health in the pas	t week?				
4	1	2	3	4	5	6		7
6	very poor" to							very good
7	30. How would	l you rate the overal	l quality of your lif	e in the past week	?			
8	1	2	2	4	5	6		7
9	1	2	3	4	5	0		/
10	very poor" to							very good
11	Patients sometim	nes have the followi	ng clinical sympton	ns. Please indicate	the extent of th	ese clinical s	ymptoms	or problems you
12	have had in the p	bast week, circling t	he answer that best	applies to you.				
14					Ν	No A little	Some	Very much
15	31. Do you cou	ıgh a lot?			1	2	3	4
16	32. Do you cou	e 19 up blood (blood	in sputum)?		1	2	3	4
17	33 Do you fee	l short of breath wh	an you rest?		1	2	3	4
18	33. Do you ice				1	2	2	4
19	34. Do you fee	I short of breath wh	en you take a walk	<u> </u>	1	2	3	4
21	35. Do you fee	l short of breath wh	en climbing stairs?		1	2	3	4
22	36. Have you e	ever had pain in you	r mouth or tongue?		1	2	3	4
23	37. Have you e	ever had difficulty sy	vallowing?		1	2	3	4
24	38. Have you e	ever had tingling/nu	nbness in your han	ds and feet?	1	2	3	4
25	39. Have you e	ever had hair loss?			1	2	3	4
20 27	40. Have you e	ever had chest pains	2		1	2	3	4
28	41 Have you e	ver had pain in you	r arms or shoulders	2	1	2	3	4
29	41. Have you e	wei had pani in you		1	1	2	2	4
30	42. Have you e	ever had any pain in	other parts of your	body?	1	2	3	4
31	If yes, please	e write down the are	ea:					
32	43. Have you e	ever taken any paink	illers?					
33 34	1.Yes		2.No					
35	If you have use	ed it, does it help mu	ch with pain?		1	2	3	4
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Supplementary 2. Breast Cancer Survival Quality Scale EORTC QLQ-BR23

Please recall if you have experienced any of these symptoms or the extent of the problem and tick the appropriate number " $\sqrt{}$ "

In the past 1 week	No	A little	More	A lot
1. Do you have dry mouth?	1	2	3	4
2. Do your food and drinks taste different than usual?	1	2	3	4
3. Do your eyes hurt, feel uncomfortable, or tear up?	1	2	3	4
4. Do you have hair loss?	1	2	3	4
5. If you have hair loss, does it bother you?	1	2	3	4
6. Do you feel sick or uncomfortable?	1	2	3	4
7. Is your face red and hot?	1	2	3	4
8. Do you have a headache?	1	2	3	4
9. Do you feel less physically attractive due to illness or treatment?	1	2	3	4
10. Do you feel less attractive as a woman due to illness or	1	2	3	4
treatment?				
11. Do you have difficulty looking at your naked body?	1	2	3	4
12. Are you dissatisfied with your body?	1	2	3	4
13. Are you worried about your future health?	1	2	3	4
In the past 4 week				
14. How interested are you in sex?	1	2	3	4
15. How active are you sexually (do you have sex often)? (With or	1	2	3	4
without sex?)				
16. If you have sex, to what extent does it bring you pleasure?	1	2	3	4
In the past 1 week				
17. Do you have pain in your arm or shoulder?				
18. Is your arm or hand swollen?				
19. Do you have difficulty lifting or moving your arm to the side?				
20. Do you have pain in the area of your affected breast?				
21. Is the area of your affected breast swollen?				
22. Do you have hypersensitivity in the affected breast area?				
23.Do you have skin problems (e.g. itching, dryness, flaking) in the				
affected breast area?				

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Supplementary 3. Evalu	ation criteria for common adverse	e events (CTCAE Version 4.	03)	9 on ling f	
(excerpt, normal commo	on adverse event evaluation criteri	a is grade 0)		or 20	
Adverse Events		1	Grading	is essered to the second secon	
	1	2	3		5
Hemoglobin g/L	Normal value -10.0	10.0-8.0	8.0-6.5	<6. 5 11 12 14	
Leukocytes(10 ⁹ /L)	Normal value-3.0	3.0-2.0	2.0-1.0		
Neutrophils(10 ⁹ /L)	Normal value-1.5	1.5-1.0	1.0-0.5		
Platelets(10 ⁹ /L)	Normal value-75	75-50	50-25	< 25 and de	
Transaminase ALT/AST	≤2.5×N	2. $6-5.0 \times N$	5.1-20×N	>20 Xata r	
Alkaline phosphatase	$\leq 2.5 \times N$	2.6-5.0×N	5.1-20×N	>20 18 16	
Bilirubin	ULN-1.5×N	1.5-3.0×N	3.0-10×N		
Creatinine Cr	ULN-1.5×N	1.5-3.0×N	3.0−10×N		
Weight gain/loss	5.0-10%	10-20%	≥20%	aini	
Vomiting	Vomiting 1 time in 24h during	Vomiting 2-5 times in	Vomiting ≥ 6 times in 24h	Life-threatening and	Death
	treatment	24h during treatment	during treatment or requiring fluids	requires urgent treatment	
Coughing sputum	Occasional/mild coughing of	Moderate cough and	Persistent heavy coughing	n Ju	
	sputum	sputum; interferes with instrumental daily life	and limited personal self-	ine 14, techne	
Pneumonia	Asymptomatic; clinical	Symptomatic (mild	Severe symptoms; limited	Life-threat sping	Death
	examination or diagnostic	cough and/or dyspnea,	personal autonomy; need for	respirerory alysfunction;	
	findings only; no intervention	with or without fever);	oxygen	requiring G gent	
	required	requires clinical		treatment (gracheotomy	
		intervention; interferes		or intubati	
		with instrumental daily		olio	

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		life		9 or	
Acute coronary		Symptomatic,	Symptomatic, unstable	Symp	Death
syndrome		progressive angina;	angina with/ or acute	angina vit	
		normal cardiac enzymes;	myocardial infarction,	myocarda binfarction,	
		hemodynamically stable	abnormal cardiac enzymatic	abnori and cardiac	
			parameters,	enzynters,	
			hemodynamically stable	hemoo kan a hemoo hemoo	
Left ventricular			Symptoms of decreased	Uncongroulgeble heart	Death
systolic insufficiency			ejection fraction	failure weth declining	
				ejection fraction	
				requir	
				intervention	
Heart Failure	Asymptomatic, with	Mild to moderate	Symptoms occur at rest or	Life-theatening; requires	Death
	abnormalities detected by	symptoms with activity	with light activity or	urgentereament (e.g.	
	laboratory tests (e.g.,	or exercise	exercise; requires treatment	contingous	
	natriuretic peptide) or cardiac			therap or nechanically	
	imaging			assister circulation)	
Limb edema	Comparison using the greatest	Comparison using the	>30% volume variation	n Ju	
	difference in volume or	largest difference in	between limbs; severe	une r tec	
	circumference, with 5% to	volume or	changes in limb shape;	14,	
	10% variation between limbs;	circumference, 10%	limited personal autonomy	202	
	edema or blurred anatomy that	<~30% difference		ies.	
	can only be detected on close	between limbs;		Age	
	examination	disappearance of skin		nce	
		folds; apparent loss of		Bit	
		limb anatomy, change in		olio	

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		shape; interferes with instrumental daily living		049 on 30 uding for	
Neurotoxicity - Sensory	Mild sensory abnormalities (including paresthesia), absence of deep tendon reflexes	Moderate objective sensory deficit or sensory abnormalities (including tingling)	Severe objective sensory loss or sensory abnormalities that affect daily life	Persis affecting	Death
Neurotoxicity-motor	Self-perceived weakness with no objective findings	Moderate self-conscious weakness; no significant functional impairment	Self-perceived weakness with functional impairment	Paraly to Superieu Paraly to Superieu and c	Death
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Supplementary 4. Scoring	g criteria for acu	ute radiation reactions (RTOG/E0	ORTC 1995)	ng fo	
Organ Tissue	0	1	2	а з больс	Δ
Skin	No change	Punctate skin erythema, alopecia, dry peeling or decreased sweating	Marked erythema, patchy wet peeling or moderate edema of the skin	Presence of fused well. 8 desquamation or sumer edema	Skin ulcers, bleeding or necrosis
Larynx	No change	Mild to moderate hoarseness/cough without cough suppressants/mucosal edema	Persistent hoarseness but vocalization/involved otalgia, sore throat, flaky	ont involved soft speech, sore the upped otalgia requiring and ur (Am	Significant dyspnea, wheezing, hemoptysis requiring tracheotomy or intubation
Pharynx and esophagus	No change	Mild dysphagia requiring general analgesia or/non- narcotic analgesia/need for semi-liquid diet	Moderate dysphagia/narcotic analgesia/fluid	narcotics / fused find by exudate, marked arytenoid generation P	Complete obstruction, ulceration ulceration, perforation, sinus tract
Lungs	No change	Mild symptoms, mild dry cough or exertional dyspnea, may be associated with imaging changes	Moderate symptoms, persistent cough requiring narcotic cough suppressant treatment or dyspnea with mild activity	Severe dysphagia thy pration or weight loss >15% Enced for gastric feeding or intraverence for gastric feeding or intraverence for gastric severe cough or depresent at rest with severe symptoms, neffective sedation or cough puppessants, clinical and imaging evolution acute pneumonia, evolution intermittent oxygen or formonal therapy	Severe respiratory insufficiency requiring continuous oxygen or assisted ventilation
Heart	No change	Asymptomatic but objective evidence of ECG changes or	Symptoms not requiring specific treatment with ECG	Congestive heart failure angina pectoris or pericardial esease for	Congestive heart failure, angina pectoris,
			n//hminnen.hmi	yraphique de l	

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Page 27 of 56		BMJ Open	bmjopei 1 by cop	
1 2 3			n-2023-07804 yright, inclu	
4 5	pericardial abnormalities, no ch	hanges and imaging	which drug therap is offective	pericardial disease or
6	evidence of other cardiac ch	hanges of congestive heart	for	arrhythmias that have not
7	disease fa	ailure or pericardial disease	동 문 년	responded to non-surgical
9			y 20 s rei	treatment
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	For peer review only - http://	/bmjopen.bmj.com/site/abou	024. Downloaded from http://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de I ignement Superieur (ABES) . elated to text and data mining, Al training, and similar technologies.	
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Organ Tissue	Grading Q							
	0	1	2		4			
Skin	No change	Mild atrophy,	Lamellar atrophy,	്റ്റ്≺ Significa∰ ഇateophy,	Ulcers			
		hyperpigmentation,	moderate capillary	marked marked				
		partial hair loss	dilatation, total hair loss	d to				
Subcutaneous tissue	No change	Mild sclerosis (fibrosis)	Moderate fibrosis but	Severe set for and loss	Necrosis			
		and loss of subcutaneous	asymptomatic, slight	of subcuence				
		adipose tissue	constriction of irradiated	Constriction of the				
			field <10% of the side	irradiate				
		Ph -	length	border le				
Lungs	No change	Asymptomatic or mildly	Moderate symptomatic	Severe semplematic	severe respiratory			
		symptomatic (dry cough),	pulmonary fibrosis or	pulmonary fierosis or	insufficiency requiring			
		mild imaging signs	pneumonia (severe	pneumon a with dense	continuous oxygenation			
			cough), hypothermia,	imaging hanges	or assisted ventilation			
			patchy imaging	an co				
Heart	No change	Asymptomatic or mildly	Moderate exertional	Severe angina pectoris;	pericardial tamponade;			
		symptomatic; temporary	angina; mild pericarditis;	pericard al effusion;	severe heart failure;			
		T-wave inversion and ST	normal heart size;	constrictive pericarditis;	severe constrictive			
		changes; sinus	persistent T-wave	moderate heart failure;	pericarditis			
		tachycardia >110	abnormalities and ST	cardiac colar ement;				
		beats/min at rest	changes; low QRS waves	abnorma				
				electrocardiogram				
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Level	Double breast	Double	Breast snape on the affected side	Skin
	symmetry	laval con		
F 11 /	<u> </u>			NT 1
Excellent,	Symmetries	≤2cm	No significant difference with the healthy	Normal
Good			side, normal appearance, no deformation of	
			the breast lift due to scarring, no difference	
			between the affected side and the healthy	
			side in feel	
General	Symmetries	2cm-	The shape of the affected breast is basically	Lightened
		3cm	normal or slightly smaller than the healthy	or shiny
			side, and the feel of the affected side is	color
			slightly worse.	
Bad	Obvious	>3cm	The appearance of the affected side of the	Thick,
	asymmetry		breast changes and is significantly smaller	rubber-
			than the healthy side, and feels poorly in the	like,
			hand	rough

Supplementary 6. Harris Cosmetic Grade Rating of Cosmetic Breast Preservation/Reconstructive
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Grading	Breast Implants
I (no accessible envelope)	Breast implants feel as soft as non-operated breasts
II(Lightly hardened)	The softness of the breast is slightly worse, the implant can be touched
	but not seen
III(Heavy hardening)	Harder breasts, implants can be easily touched out or visible
	deformation of the implant
IV(severe contracture)	Breasts are hard, painful when touched, skin temperature becomes
	cold, deformation is obvious

Only Baker grade III and IV are defined as periosteal contracture and require reoperation

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Supplementary 8. Radiotherapy-related adverse reactions and their treatment

1 Radiation-induced skin damage

Early skin reactions are those that occur within three months after the start of radiotherapy and are the most common complications in breast radiotherapy. Approximately 92% of patients receiving postlumpectomy radiotherapy will experience acute radiation-induced skin reactions, mostly grade 1 or 2 mild reactions, with a wet desquamation incidence rate of about 3%. Patients undergoing mastectomy will almost always experience acute radiation-induced skin reactions, mostly grade 2 reactions, with a wet desquamation incidence rate of about 10-20%.

Prevention is the main approach to managing radiation-induced skin complications. For grade 1 and 2 injuries, conservative treatment is primarily used. Patients should wear loose, cotton open-front underwear, avoid friction and pressure on the skin in the irradiation area, avoid using irritating products such as soap and shower gel, avoid bathing with hot water or showering the irradiation area, and not apply chemical ointments or adhesive tape. If the skin is red, swollen, itchy, or painful, do not scratch it or apply medication randomly. Follow the doctor's advice for medication, such as triethanolamine cream, compound vitamin B12 solution, and medical radiation protectants. Wet dermatitis can be treated with exposure therapy, keeping the area dry and avoiding secondary infections. Wet dermatitis that does not heal after more than two months may develop into skin necrosis, often requiring surgical treatment, with skin grafting for larger areas.

Late skin reactions include local hyperpigmentation, telangiectasia, atrophy, and fibrosis. For chronic radiation dermatitis with recurrent ulceration and significant worsening, surgery is often used to prevent malignant transformation.

2 Pharyngeal and esophageal reactions

Irradiation of the supraclavicular area can cause pharyngeal pain and difficulty swallowing, which are generally mild and self-limiting. Prevention methods include using new radiotherapy techniques, accurate positioning, precise delineation of the target area, rational design of radiation fields, and reducing or avoiding irradiation of organs at risk. Symptomatic support treatment is provided for severe reactions.

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3 Radiation-induced lung injury

Radiation-induced lung injury includes early radiation pneumonitis occurring within 3 months after radiotherapy and late radiation-induced pulmonary fibrosis occurring after 3 months. Approximately 2/3 of patients will develop asymptomatic radiation pneumonitis, which does not require treatment. The incidence of symptomatic radiation pneumonitis is between 1% and 5%, usually occurring within 2 months after radiotherapy or within 6 months after radiotherapy. Patients have symptoms and signs of pneumonia, which can manifest as cough, sputum, or fever, and in severe cases, dyspnea and hypoxia. In particular, when imaging examinations (chest X-rays and CT scans) show inflammatory exudative changes in the lung tissue within the irradiation field, symptomatic radiation pneumonitis can be diagnosed after excluding lung metastasis and tuberculosis. Supportive treatment, including hormones, oxygen therapy, and even mechanical ventilation, can provide complete relief, but some patients may still develop pulmonary fibrosis within 6-12 months, even with treatment. Pulmonary fibrosis is a late injury caused by damage to the lung interstitium and pleura, and in severe cases, it can be life-threatening.

There is currently no specific treatment for radiation pneumonitis, so prevention is more important than treatment. For patients undergoing whole-breast irradiation alone, it is recommended to use a dose-volume constraint of V20 < 22% for the ipsilateral lung. For those receiving irradiation of the supraclavicular lymph node region, a dose-volume constraint of V20 < 34% and V30 < 22% should be used for the ipsilateral lung to further evaluate the overall radiotherapy plan.

4 Radiation-induced heart damage

Radiation-induced heart disease (RIHD) initially manifests as acute pericarditis and later as coronary artery disease, chronic pericarditis, myocardial fibrosis, cardiomyopathy, heart valve damage, and cardiac conduction abnormalities. A 2013 New England Journal article reported that for every 1 Gy increase in the average dose to the heart, the incidence of major coronary events increased by 7.4%. Reducing the risk of RIHD is also focused on prevention. The most fundamental measure is to minimize or avoid radiation exposure to the heart during radiotherapy. The Chinese Anti-Cancer Association Breast Cancer Diagnosis and Treatment Guidelines and Standards (2015 Edition) recommend that the average radiation dose to the heart should be assessed to be at least below 8 Gy. It is recommended to limit the heart's V30 to less than 10%. In addition, for high-risk populations of RIHD or those with cardiovascular disease, drugs that have a protective effect on the cardiovascular system should be used as soon as possible. Regular cardiac ultrasound follow-ups should be conducted during the follow-up phase.

5 Upper limb edema

Edema in the affected upper limb is one of the common complications after breast cancer surgery and/or radiotherapy, and the extent of surgery is an important influencing factor. AMAROS research reported that the 1-year, 3-year, and 5-year lymphedema incidence rates for the ALND group were 28%, 23%, and 23%, respectively, significantly higher than the 15%, 14%, and 11% for the SLNB + axillary radiotherapy group. The incidence of upper limb lymphedema after axillary lymph node biopsy alone is 5%. Edema caused by radiotherapy usually occurs 1 to 2 months after the end of radiotherapy. Depending on the time of onset, upper limb edema caused by tumor recurrence in the axilla and supraclavicular region is not considered a true post-treatment complication.

The main prevention method for upper limb edema is to reduce axillary dissection, and postoperative progressive functional exercise is the key to preventing upper limb edema. When upper limb edema occurs, manual massage or compression therapy can be used.

6 Brachial plexus nerve injury

Radiation-induced brachial plexus nerve injury is a rare late complication after breast cancer radiotherapy, with an incidence rate of 1%-4%. Early symptoms include sensory and motor disorders in the affected limb and pain, often accompanied by severe nocturnal pain. Some cases may also have lymphedema, with progressively worsening functional impairment. In the late stage, this can lead to the loss of function of the entire limb, causing lifelong disability for the patient and severely affecting the patient's daily life and rest, with a significant impact on their mental health and quality of life. A preliminary diagnosis can be made based on the patient's radiotherapy history, asymptomatic intervals, and clinical features in clinical practice. However, it is necessary to rule out brachial plexus nerve injury caused by tumor metastasis or compression.

Radiation-induced brachial plexus nerve injury is irreversible, and there is currently no ideal treatment

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method, so prevention is crucial. It is essential to strictly follow the indications for radiotherapy in the lymphatic drainage area and pay attention to the radiotherapy range and radiation dose. For cases without severe pain, active measures should be taken to improve the blood supply of the nerves and surrounding soft tissues, and the earlier the diagnosis and treatment, the better the results. For advanced cases, treatment is aimed at relieving pain and improving quality of life.

7 Second primary tumors

Second primary tumors that can occur after breast cancer treatment include contralateral breast cancer and other malignant tumors such as lung cancer and soft tissue sarcomas. If these second primary tumors can be diagnosed and treated early, they do not affect the patient's survival. Therefore, regular follow-up of patients should be strengthened in clinical practice.

8 Rib fractures

The incidence is less than 1%. In most cases, patients have no noticeable symptoms, and fractures are discovered during bone scans or X-ray examinations. A small number of patients may experience chest wall or rib pain, which generally heals on its own without the need for special treatment.

9 Other side effects

During radiotherapy, patients may experience mild loss of appetite and fatigue. Therefore, it is important to adjust the diet reasonably, advocating for a "high protein, high vitamin, low fat" diet to maintain a balanced nutrition. Regularly review routine blood tests, and if a decrease in white blood cells is found, there is a risk of infection. In such cases, it may be necessary to temporarily pause radiotherapy and follow the doctor's advice for symptomatic supportive treatment.

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Supplementary 9 Guidelines for Target Volume Delineation

Clinical practice involves the use of RNI+WBI(BCS)/CWI (complete mastectomy) in patients who are of low-risk clinically but high-risk in terms of RecurIndex LR.

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- 1.1 Whole Breast Clinical Target Volume (CTV_2)
 - 1. Purpose: Applicable for patients who undergo breast conservation surgery and axillary lymph node dissection.
 - 2. Target definition: The entire or majority of the mammary gland on the affected side, encompassing the entire tumor bed target range, entire retro mammary space and pectoralis major fascia, Rotter's lymph nodes in the pectoralis major and minor inter-space, and the mid and lower axilla within the entire breast target range that was not cleared.
 - 3. Target boundaries: The upper boundary is the palpable/CT-visible upper edge of the gland. The lower boundary is the palpable/CT-visible lower edge of the gland. The anterior boundary is 5mm subcutaneously, or 0.3cm subcutaneously or even up to the skin for thin and small breasts. The posterior boundary is 1-2mm behind the surface of the pectoralis major fascia (adjacent to the retro mammary space), not leaving a fatty gap, excluding ribs/intercostal muscles, but including Rotter's lymph nodes and axillary regions I and II if regional lymph nodes are metastatic. The medial boundary is next to the sternum, at least to the inner edge of the gland, anterior to the thoracodorsal artery, anterior edge of the latissimus dorsi muscle.

1.2 Tumor Bed and CTV_1

- Purpose: Applicable for patients undergoing breast-conserving surgery. Boost to the tumor bed is not mandatory and is determined by the policy of each center. Boost is suggested under the following circumstances: positive margin, close margin (invasive cancer or DCIS with a negative margin ≤2mm), and young age (<50 years).
- 2. Tumor bed definition: The range of the excised tumor and its surrounding tissue cavity, filled with serous effusion or formed tissue.
- 3. Tumor bed boundaries: Refer to: (1) The location of titanium clips, with a suggestion of placing clips at the left, right, top, bottom, and rear (2) The range of serous effusion, including that within the gland and sub-scar.
- 4. Tumor Bed CTV_1: Includes the mammary gland and soft tissues 10-15mm beyond the surgical excision of the tumor bed. It is suggested to reduce this for patients undergoing segmental resection to about 10mm. If there is no gland beyond the tumor bed, consider reducing it; for positive margins or presence of EIC or severe ADH, it is crucial to appropriately increase the range.

1.3 Integrated Target Area of the Whole Breast and Lower and Middle Axillary CTV_2

- 1. Purpose: Applicable for patients undergoing breast conservation surgery plus sentinel lymph node biopsy.
- 2. Target definition: Whole breast + axillary lymph nodes in zones I and II + Rotter's lymph nodes between pectoralis major and minor muscles.
- 3. Target boundaries: Whole breast boundaries refer to 5.2.3.1.1 Whole Breast Target; axillary zone I: Anatomically marked by the pectoralis minor muscle, located laterally to the pectoralis minor; axillary zone II: Follows the course of the axillary vein, located posterior to the pectoralis minor including the intermuscular space of pectoralis major and minor (Rotter's

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LN).			
Criterion	Axillary Zone I	Axillary Zone II	Rotter's Lymph Nodes
Superior	Where the axillary vessels cross	Where the axillary vessels	Including the cephalic side of
Boundary	the lateral edge of the pectoralis	cross the medial edge of the	the axillary artery and 5mm
	minor muscle	pectoralis minor muscle	above the axillary vein
Inferior	Where the pectoralis major	Where the axillary vessels	Inferior boundary of axillary
Boundary	muscle inserts into the rib	cross the lateral edge of the	zone II
		pectoralis minor muscle	
Anterior	Anterior to the pectoralis major	Anterior to the pectoralis minor	Posterior to the pectoralis
Boundary	muscle and latissimus dorsi	muscle	major muscle
	muscle		
Posterior	Anterior to the subscapularis	Rib and intercostal muscles	Anterior to the pectoralis minor
Boundary	muscle		muscle
Medial	Lateral edge of the pectoralis	Medial edge of the pectoralis	Medial edge of the pectoralis
Boundary	minor muscle	minor muscle	minor muscle
Lateral	Medial aspect of the latissimus	Lateral edge of the pectoralis	Lateral edge of the pectoralis
Boundary	dorsi muscle	minor muscle	minor muscle
1 4 01' ' 1 T		T)	

1.4 Clinical Target Volume for Chest Wall (CTV_CW)

1. Purpose: Applicable to patients who have undergone total mastectomy ± breast reconstruction surgery.

2. Target Definition: The surgical area that may cause intraoperative spread and carry the risk of recurrence after total mastectomy.

3. Target Boundaries • Upper boundary is a clinical marker/0.5-1cm below the clavicle head; • Lower boundary is a clinical marker/below the contralateral breast fold; • Anterior boundary is the skin, excluding lead wire; • Posterior boundary is the intercostal muscle of the rib; • Medial boundary is a clinical marker/at the junction of the sternum and ribs; • Lateral boundary is a clinical marker/ at the anterior edge of the thoracic and dorsal vessels and the latissimus dorsi.

Note: ① Includes all scars, with the target area 2cm above and below the scar not reduced; ② Includes postoperative changes observed on CT scan (granuloma and fibrotic changes, barb-like muscle irritation signs).

1.5 Clinical Target Volume for Supraclavicular and Infraclavicular Lymph Nodes (CTV_LN)

- 1. Purpose: Suitable for group A patients with low clinical risk and high RecurIndex LR risk requiring regional lymph node radiation.
- 2. Target Definition: Includes supraclavicular area, neck IV region, and infraclavicular lymph nodes (unsurgically treated Level III axillary lymph nodes).
- 3. Target Boundaries Upper boundary is below the cricoid cartilage; Lower boundary is 0.5-1cm below the clavicle head, where the subclavian vein disappears, and connects with the whole breast/chest wall target area; • Anterior boundary is behind the sternocleidomastoid muscle above and behind the pectoralis major muscle below; • Posterior boundary is the posterior edge of the anterior scalene muscle above and the anterior edge of the rib and intercostal muscle below; • Medial boundary is the internal jugular vein above, including the entire scalene muscle gap to the level of the transverse cervical artery and vein, and the junction of the subclavian vein and internal jugular vein below; • Lateral boundary is the

lateral edge of the sternocleidomastoid muscle above and the lateral edge of the pectoralis minor muscle below.

• Note: ① Avoid the operated axillary area (Level I and part of Level II); ② Includes the unsurgically treated axillary Level II area.

1.6 Internal Mammary Lymph Node Area (CTV_IMN)

- Purpose: Applicable to Group A patients with low clinical risk and high RecurIndex LR, requiring regional lymph node irradiation. Irradiation of the internal mammary lymph node region is not obligatory and is determined by the radiation oncologist.
- Target area definition: Those at risk of internal mammary lymph node metastasis may benefit from internal mammary lymph node irradiation. It includes the 1st-3rd intercostal spaces, 5mm in all directions from the intrathoracic vessels, the upper boundary infusing into the supraclavicular area, and the lower boundary at the upper edge of the 4th rib.
- 3. Target area boundaries: Superior border: Infusion into the supraclavicular area; Inferior border: Upper edge of the fourth costal cartilage; Anterior border: Back of the pectoralis major muscle, back of the sternum; Posterior border: Pleura or 5mm behind the internal mammary vessels; Medial border: 5mm inside the internal mammary vessels, including the whole space between the sternum and vessels; Lateral border: 5mm outside the internal mammary vessels, outer edge of the brachiocephalic vessels.
 - Note: ① For high-risk patients, the upper boundary extends to the junction of the internal jugular vein, subclavian vein, brachiocephalic vein, and internal mammary vein; ② It is recommended to expand at least 5mm inside and outside the direction of the internal mammary vessels.
- 1.7 Intraclavicular Lymph Nodes (CTV_intraclavicular-LN)
 - 1. Purpose: Applicable to Group A patients with low clinical risk and high RecurIndex LR, requiring regional lymph node irradiation. Irradiation of the intraclavicular lymph node area is not obligatory and is determined by the radiation oncologist.
 - 2. Target area definition and boundaries: Those at risk of intraclavicular lymph node metastasis may benefit from intraclavicular lymph node irradiation. The upper boundary is the horizontal level of the transverse cervical artery, the lower boundary is the upper edge of the brachiocephalic trunk, the medial boundary is the midline of the body, and the lateral boundary is the inner edge of the supraclavicular area.
 - Note: ① When irradiating the internal mammary lymph nodes, it should be routinely outlined; ② When there is metastasis of supraclavicular lymph nodes, it should be routinely outlined; ③ When there is extracapsular invasion of axillary Level II/III lymph nodes, it should be routinely outlined; ④ In patients with primary tumors invading the deep fascia, or the primary lesion located in the medial and upper part of the breast, consider outlining.

In patients who are clinically low-risk but exhibit a high-risk RecurIndex LR, regional nodal irradiation (RNI) is omitted, with whole breast irradiation (WBI) after breast-conserving surgery (BCS) only and no chest wall irradiation (CWI) after total mastectomy.

- 2.1 Entire Breast Target Volume (CTV_2):
 - 1. Purpose: Suitable for patients who have undergone breast conservation surgery with axillary lymph node dissection.
 - 2. Target Definition: This includes all or most of the glandular tissue of the affected breast, encompassing the entire tumor bed, the entire space posterior to the breast and the pectoral

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fascia, the interpectoral space (Rotter's lymph nodes), and any unswept low-mid axilla within the entire breast target volume.

3. Target Borders: • Superior border is the palpable/visible edge of the glandular tissue on CT. • Inferior border is the palpable/visible lower edge of the glandular tissue on CT. • Anterior border is 5 mm below the skin, but for small or thin breasts, it should be adjusted to 0.3 cm below the skin or even closer. • Posterior border is 1-2 mm behind the pectoral fascia (adjacent to the space below the breast), with no fat gap left and no inclusion of ribs/intercostal muscles. If regional lymph nodes have metastasized, include interpectoral lymph nodes and unswept axillary regions I and II. • Medial border is next to the sternum, extending at least to the inner edge of the peristernal vessels. • Lateral border is the palpable or CT-visible outer edge of the glandular tissue, anterior to the dorsal thoracic artery, anterior edge of the latissimus dorsi muscle.

2.2 Tumor Bed and CTV1:

- Purpose: Suitable for patients who have undergone breast-conserving surgery. Boosting of the tumor bed is not mandatory and depends on the policy of each center. Boosting of the tumor bed is recommended under the following conditions: positive surgical margins, close margins (invasive cancer or DCIS with negative margins ≤2 mm), young age (<50 years).
- 2. Tumor Bed Definition: The area where the tumor and surrounding tissue have been excised, filled with serum exudate or plastic tissue.
- 3. Tumor Bed Borders: Based on the location of the titanium clips. It is suggested that titanium clips be placed in five directions: left, right, up, down, and behind. The extent of serum exudate, taking into account any within the glandular tissue and beneath the scar.
- 4. Tumor Bed CTV_1: Includes the resected tumor bed extended by 10-15 mm into the glandular breast tissue and soft tissue. For patients undergoing segmental resection, this may be appropriately reduced, with a suggested 10 mm. If there's no glandular tissue outside the tumor bed, consider reducing it. In case of positive margins or presence of extensive intraductal component (EIC), severe atypical ductal hyperplasia (ADH), the range must be appropriately expanded.

2.3 Integrated Target Volume of the Entire Breast and Low-to-Mid Axillary Region (CTV_2):

- 1. Purpose: Suitable for patients who have undergone breast conservation surgery with sentinel lymph node biopsy.
- 2. Target Definition: The entire breast + lymph nodes in axillary regions I and II + interpretoral lymph nodes (Rotter's lymph nodes).
- 3. Target Borders: For the entire breast, refer to Section1.1 Entire Breast Target Volume; Axillary Region I: anatomically marked by the small pectoral muscle, located on the lateral side of the muscle; Axillary Region II: follows the axillary vein, located posterior to the small pectoral muscle, and also includes the interpectoral space (Rotter's LN).

Boundary	Axillary Region I	Axillary Region II	Rotter's Lymph Nodes	
Superior	Where axillary vessels cross the	Where axillary vessels cross	Including the cranial side of the	
Border	lateral edge of the small pectoral	the medial edge of the small	axillary artery and 5 mm above	
	muscle	pectoral muscle	the axillary vein	
Inferior	Where the large pectoral muscle	Where axillary vessels cross	Inferior border of axillary region	
Border	inserts into the rib	the lateral edge of the small	II	
		pectoral muscle		

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		1	1
Anterior	In front of the large pectoral and	In front of the small pectoral	Behind the large pectoral muscle
Border	latissimus dorsi muscles	muscle	
Posterior	In front of the subscapularis	Ribs and intercostal muscles	In front of the small pectoral
Border	muscle		muscle
Medial	Outer edge of the small pectoral	Inner edge of the small	Inner edge of the small pectoral
Border	muscle	pectoral muscle	muscle
Lateral	Inner surface of the latissimus	Outer edge of the small	Outer edge of the small pectoral
Border	dorsi muscle	pectoral muscle	muscle

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2			
3	Supplementary 10 Dose distribution and organ endangerment limits		
4 5	Target Volume	Dmax	Dmin
6	Whole Breast PTV_2	≤107%	≥90%
7	Tumor Bed PTV_1	≤107%	≥90%
8 9	Whole Breast and Low-to-Mid Axilla Integrated Target Volume PTV_2	≤107%	≥90%
10	Chest Wall PTV_CW	≤110%	≥90%
11 12	Supraclavicular (±intranodal clavicular) PTV_LN	≤110%	≥90%
12	Internal Mammary PTV_IMN	≤110%	≥80%
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Organs	Volume	Type of	Observation	Dose (Gy)	Incidence	Dose volume
		irradiation	index	or dose	(%)	parameter
		(partial		volume		description
		organ or		parameter		
		specially				
		indicated)				
Spinal	Partial	3DCRT	Spinal cord	Dmax=50	0.02	Includes all
Cord	spinal cord		lesions			spinal cord
	Thoracic					cross-sections
	medulla					
Pharynx	pharyngeal	3DCRT	Dysphagia	Dmean<	<20	
	constrictor		and	50		
	muscle		shortness of			
			breath			
larynx	Total larynx	3DCRT	Edema	Dmean<	<20	No
				44		chemotherapy,
	Total larynx	3DCRT	Edema	V50<27%	<20	based on a
						single study of
						patients
						without
						laryngeal
						cancer
lung	whole lung	3DCRT	Pneumonia	V20≤30%	<20	Double lung.
	whole lung	3DCRT	Pneumonia	Dmean=7	5	Slow dose
	whole lung	3DCRT	Pneumonia	Dmean=13	10	response
	whole lung	3DCRT	Pneumonia	Dmean=20	20	Without whole
	whole lung	3DCRT	Pneumonia	Dmean=24	30	lung treatment
	whole lung	3DCRT	Pneumonia	Dmean=27	40	irradiation
Esophagus	Whole	3DCRT	≥3 Grade	Dmean<	5-20	Contains
	Esophagus		acute	34		various dose
			esophagitis			limiting
	Whole	3DCRT	\geq grade 2	V35<50%	<30	factors. Seems
	Esophagus		acute			to be related to
			esophagitis			dose volume
	Whole	3DCRT	\geq grade 2	V50<40%	<30	
	Esophagus		acute			
			esophagitis			
heart	Pericardium	3DCRT	pericarditis	Dmean<	<15	Based on
				26		individual
	Pericardium	3DCRT	pericarditis	V30<46%	<15	studies
	W/h = 1 = 1 = = = = = =	1DODT	1	V25 / 160/	<1	ILiah
-	whole heart	3DCR1	distant	V23~40%	~ 1	підп

Supplementary 1	1. Organ	dose/volume	e/impact d	lata for	routine	split	exposures	(except	where	noted):
QUANTEC										

			death			assessing
						security based
						on predictive
						models
Liver	Whole	3DCRT	Typical	Dmean<	<5	Exclude
	Liver - GTV		RILD	30-32		patients with
						existing liver
						disease or
						liver cancer
	Whole	3DCRT	Typical	Dmean<	<50	Patients with
	Liver - GTV		RILD	42		liver disease
	Whole	3DCRT	Typical	Dmean<	<5	or
	Liver - GTV		RILD	28		hepatocellular
	Whole	3DCRT	Typical	Dmean<	<50	carcinoma
	Liver - GTV		RILD	36		with a Child-
						Pugh rating of
						A, but not
						active
						hepatitis B,
						were included
						as observation
						indicators
	Whole	3DCRT	Ulcer	D100<45	<7	
	stomach			•		

QUANTEC: Quantitative Analysis of Illumination Response in Clinically Normal Tissues; 3DCRT: Three-Dimensional Conformal Radiotherapy; GTV: Gross Tumor Volume; RILD: Radioactive Liver Injury; RTOG: Radiation Therapy Oncology Group of Amer

Page 42 01 50	Page	42	of	56
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upplementary 12. Research	Schedule										(3-078049 or t. including				
Research Phase	Screening		Radiother	apy perio	d					Fol	llow up p	e riode				
Visits	1	2	3	4	5	6	7	8	9	10	11	ليرا) En	13	14	15	
Time	-3M-0	1W	2W	3W	4-7W	6M	12M	18M	24M	30M	36M	v 2024.⊉ownlo seignement Su s related to tex	48M	54M	60M	In the event of a relapse
Informed consent	×			r								ade uper				
Inclusion/exclusion criteria	×				Po							d from leur (AE				
Frozen/paraffin tissue	×					7L										
Pathology	×*						4				ģ	ng. · br				
Tumor markers	×					×	×	×	×	×	×	njor ×I	×	×	×	×
Breast + LN ultrasound/MR	×					×	×	×	×	×	×	ven.bm	×	×	×	
Mammography	×*						×		×		×	and Co	×		×	
Chest X-ray/CT	×					×	×	×	×	×	×	sir ×o	×	×	×	×
Abdominal ultrasound/CT	×					×	×	×	×	×	×	n June ×une	×	×	×	×
Thyroid + LN ultrasound	×					×	×	×	×	×	×	14, 202! × 202!	×	×	×	
Bone Scan	×*						×		×		×	es. at	×		×	×
Cranial CT/MRI												Age				×***
Demographic features	×											nce				
Medical history	×											Bib				
Physical examination	×	×	×	×	×	×	×	×	×	×	×	×io	×	×	×	

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												en-2023-0780 pyright, inclu			
Upper and lower arm circumference measurement •	×				×		×		×		×	049 on 30 Jul Er uding for use	×		×
Body weight	×				×		×		×		×	y 20 Sei	×		×
ECOG score	×				×		×		×		×)24. gnei ilate	×		×
Blood count	×**	×	×	×	×	×	×	×	×	×	×	id nem to	×	×	×
Liver and kidney function	×**			~	×	×	×	×	×	×	×	vnloade t Super text an	×	×	×
Infectious disease	×*											d fro d da			
Serum pregnancy test	×**				2							An (AE			
EORTC QLQ-C30	×**				×	NA	×		×		×	nini	×		×
EORTC QLQ-BR23	×**				×		×		×		×	ng,	×		×
Harris	×**					4	×		×		×	Njop Al tr	×		×
Baker	×**						×		×		×	aini	×		×
CTCAE V4.03	×**	×	×	×	×		×	×	×		×	ng,	×		×
Acute radiation reaction		×	×	×	×				4			com/ o and sin			
Late radiation injury							×	×	×		×	n Ju	×		×
 Upper and lower are elbow epicondyle. * Within 12 months present within 14 days bef *** When cranial symptotic symptot sympto	m circumfer rior to rando ore randomi uptoms were	ence measu mization zation present	rements: mo	easured at	the bilater	al metacar	pophalang	eal joints (mid-metac	carpal), at t	he wrist,	næ14, 2025 at Age technologies.	he distal 10 c	m and proy	kimal 15 c
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Supplementary 13. Physical status ECOG scoring criteria

ECOG scoring criteria	Scoring
Mobility is completely normal and does not differ in any way from that before the	0
onset of the disease	
Can walk freely and perform light physical activities, including general housework	1
or office work, but cannot perform heavier physical activities	
Able to walk freely and take care of themselves, but have lost the ability to work,	2
and can get up and move around at least half of the time during the day	
Only partially able to take care of themselves, bedridden or wheelchair bound for	3
more than half of the day	
Bedridden and unable to care for themselves	4
Death	5

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Data category	Information
Primary registry and trial identifying number	Line 44 page 4
Date of registration in primary registry	7 July. 2022
Source(s) of monetary or material support	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
Primary sponsor	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
Secondary sponsor(s)	the Jiangsu Simcere Pharmaceutical Co., Ltd., Jian
	Simcere Diagnostics Co., Ltd
Contact for public queries	Xiaobo Huang, MD. [huangxbo@mail.sysu.edu.cn]
Contact for scientific queries	Xiaobo Huang, MD. Sun Yat-Sen Memorial Hospital, Sur
	Yat-Sen University, Guangzhou, Guangdong, China
Public title	RIGAIN Study
Scientific title	Line 3 page 3
Countries of recruitment	Line 29 page 4
Health condition(s) or problem(s) studied	Regional lymph node irradiation
Intervention(s)	Line 26 page 4
Key inclusion and exclusion criteria	Table 1 Line 3 page 18
Study type	Line 27 page 4
Date of first enrolment	Line 38 page 4
Target sample size	Line 33 page 4
Recruitment status	Recruiting
Primary outcome(s)	Line 19 page 8
Key secondary outcomes	Line 19 page 8

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Supplementary 14. Trial registration data

Supplementary 15. Statistical Analysis

1. Population Analysis

Full Analysis Set (FAS): Efficacy analysis will be conducted for all cases randomized according to the intention-to-treat (ITT) principle, and analyzed based on their randomized groups, regardless of the actual radiation therapy group received.

Per-Protocol Set (PPS): Subjects from the FAS set will be excluded if they have major protocol violations that could potentially affect the primary efficacy endpoint IDFS analysis. Efficacy evaluation for this study will be conducted for both FAS and PPS sets, with FAS serving as the primary analysis set.

Safety Set (SS): All subjects randomized and receiving at least one session of radiation therapy belong to the safety analysis set. This dataset utilizes actual radiation therapy groups and is used for safety analysis.

2. Demographic and Baseline Characteristics

Descriptive statistical analysis will be conducted for demographic characteristics such as age, gender, height, weight, as well as other baseline features including medical history.

3. Participant Distribution

Descriptive statistical analysis will be performed on participant enrollment status, study completion status, premature study withdrawal, etc. A tabular summary will outline the distribution of participants across different analysis populations.

4. Efficacy Analysis

Efficacy analysis will be based on both FAS and PPS, with FAS serving as the primary analysis set. Primary Endpoint Analysis: Invasive Disease-Free Survival (IDFS) serves as the primary efficacy endpoint of this study, defined as the time from randomization to the earliest occurrence of invasive cancer local recurrence, distant metastasis, or death, whichever comes first. The occurrence of invasive disease recurrence will be determined by the assessment results obtained by an independent review committee using pathological or imaging examinations. Patients who have not experienced invasive cancer local recurrence, distant metastasis, or death will have their last follow-up date considered as the censoring date. Patients who have not undergone imaging follow-up after baseline will have the randomization date considered as the censoring date. Cox proportional-hazards model will be used for the analysis of the primary endpoint to calculate the Hazard Ratio and its 95% confidence interval, adjusting for stratification factors and other covariates. Additionally, a Cox proportional-hazards model without covariates will be used to support the analysis results of the primary endpoint. Furthermore, the median invasive disease-free survival for both groups (Group A vs. Group B) will be calculated using the Kaplan-Meier (KM) method, including the 95% confidence interval. KM plots will be used to illustrate the trend of IDFS over time.

Secondary Endpoint Analysis: The analysis will compute the Annual Failure Rate (AFR) for each group, along with the corresponding 95% Clopper-Pearson confidence interval. Local recurrence-

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free survival (LRFS), distant metastasis-free survival (DMFS), relapse-free survival (RFS), overall survival (OS), disease-free survival (DFS), and breast cancer-specific mortality (BCSM) will be analyzed using the KM method to determine the median values (including the 95% confidence interval). Changes in total scores of EORTC QLQ-C30 and EORTC QLQ-BS23 from baseline will also be summarized.

5. Safety Analysis

Safety analysis will be based on the Safety Set (SS).

The safety analysis will include all enrolled patients who have received at least one session of radiation therapy, grouped according to the actual treatment received by the patients.

Safety will be assessed by summarizing adverse events, changes in laboratory test results, vital sign changes, and exposure to study treatment, reported by treatment group.

All adverse events (AEs) will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) Acute Radiation Morbidity Scoring Criteria (1995), and RTOG/EORTC Late Radiation Morbidity Scoring Criteria (1995). All adverse events occurring during treatment (Treatment Emergent Adverse Events, TEAEs, defined as events occurring within 30 days after the end of the last radiation therapy session), TEAEs of Grade 3 or higher, serious adverse events (SAEs), radiation-related SAEs, and TEAEs leading to trial discontinuation will be summarized by system organ class, preferred term, and group in terms of number and percentage. Additionally, the severity and relatedness of TEAEs to radiation therapy will also be summarized by system organ class, preferred term, and group. If a patient experiences the same adverse event multiple times, the maximum reported severity will be used for summarization.

6. Exploratory Studies

Exploratory studies will investigate the relationship between peripheral blood T lymphocyte subsets and the immunomodulatory effects of radiotherapy, as well as the relationship between circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and distant tumor eradication effects.

7. Interim Analysis

Interim analysis is not planned for this trial.

8. Final Analysis

The final analysis for this study is planned to be conducted when the last enrolled patient completes radiotherapy and reaches a follow-up of 5 years.

Supplementary 16. Data Management

1. Source Data Recording

Monitoring personnel will verify source data to confirm that the data entered by authorized personnel at the trial center into the electronic Case Report Form (eCRF), i.e., the source data, is correct, complete, and indeed originated from the source documents.

Source documents (paper or electronic) refer to patient data recorded at the earliest time and include but are not limited to: hospital records, laboratory records, memos, patient-reported outcomes, assessment checklists, data recorded on automated instruments, microfiche, photographic films, Xrays, etc.

Source documents requiring verification of data integrity and validity must not be altered or destroyed and must be retained in accordance with the applicable regulatory retention policies.

For source data verification, investigators and trial institutions must provide monitoring personnel with direct access to relevant source documents and reports for audit purposes and Institutional Ethics Board/Ethics Committee (IEB/EC) review. Trial centers must also allow regulatory authorities to conduct inspections.

2. Use of Computer Systems

When clinical observation results are entered directly into the computerized medical record system of the study center, electronic records may be considered as source documents if the system has been validated according to regulatory requirements for computerized systems adopted in clinical research. Original data should be saved using appropriate computerized data collection systems. If original data requires modification, the system must retain visual inspection audit trails showing the original data and reasons for modification, along with the names and dates of modification.

3. Case Report Forms

This study utilizes electronic Case Report Forms (e-CRFs) for data collection, completed using the Electronic Data Capture (EDC) system specified by the principal investigator. The designated vendor appointed by the principal investigator will provide training to trial centers and a suitable e-CRF completion manual to the research centers.

All e-CRFs are completed by designated, trained personnel at the trial center, and the investigator or designated personnel must review, electronically sign, and date the e-CRFs.

4. Data Quality Assurance

The clinical trial office where the principal investigator is located is responsible for data management for this study, including monitoring/audit of data quality. Clinical research data will be collected via eCRFs using the EDC system. Data entry into the ECD system will be the responsibility of the research center. In case of discrepancies, the clinical trial office where the principal investigator is located will request explanations from the research center, and this process will be electronically resolved within the EDC system.

The sponsor will develop an EDC study quality standards document outlining methods for quality checks on the data.

Data from center laboratories will be sent directly to the principal investigator, who will process and electronically transfer these data according to the standard operating procedures recognized by the

principal investigator for center laboratories.

e-CRFs and correction documents will be retained in the EDC system during the auditing process. The data retained by the principal investigator will be systematically backed up according to standard operating procedures recognized by the principal investigator for the vendor, and records of research data retention will be kept.

5. Independent Data Safety Committee

A Data Safety Committee will be established, consisting of an odd number of members (typically 5), who are independent of the project team and have signed confidentiality agreements. The committee will primarily conduct a review analysis of positive results (subject relapse and metastasis) and understand the actual study results (without statistical analysis) when half of the subjects are enrolled, voting on whether adjustments to the study protocol are necessary

Supplementary 17. Quality Management Plan

1 Quality Control

- 1) Qualifications of Study Personnel: All personnel involved in this trial, including investigators, nurses, statisticians, clinical trial observers, etc., must undergo clinical trial training and work under the guidance of senior professionals.
- 2) Investigators and other personnel involved in the study should fulfill their responsibilities and strictly adhere to the clinical trial protocol, employing standard operating procedures to ensure the implementation of quality control and quality assurance systems.
- 3) All observed results and findings in the clinical trial should be verified, and quality control must be conducted at every stage of data processing to ensure data integrity, accuracy, authenticity, and reliability.
- 4) Investigators and other personnel involved in the study should have sufficient time and reliable sources of subjects for conducting the study.
- 5) All projects involving imaging and laboratory testing should be carried out by units that comply with national standards.
- 6) Specimens requiring collection in this study should be collected by designated individuals, and follow-up data should be collected and stored by designated personnel.
- 7) Testing procedures should be conducted according to the specified Standard Operating Procedures (SOPs).
- 8) When modifications to the study protocol are required, the Ethics Committee should be convened according to SOPs, fully utilizing the Ethics Committee's functions to ensure the protection of subjects' interests.
- 9) Each participating unit should establish a file folder, save all original materials as required in the protocol, and arrange them in chronological order for verification purposes.
- 10) Contract research organizations must appoint trained monitors for the study, who should have relevant medical and pharmaceutical backgrounds, and conduct inspections of the research projects according to SOPs (including: pre-trial visits, initiation visits, routine monitoring visits, and end-of-study visits; see "Monitoring Plan").
- 11) Inspectors should systematically examine clinical trial-related activities and documents to assess whether the trial is conducted in accordance with the protocol, SOPs, and relevant regulatory requirements, and whether trial data are recorded in a timely, truthful, accurate, and complete manner. Inspections should be conducted by personnel not directly involved in the clinical trial.
- 12) The establishment of inspection work is to ensure that clinical trials are conducted in accordance with the requirements of the protocol, SOPs, and relevant regulations. Contents include: a) How is the clinical research operated? b) Is the implementation in line with the requirements of the study protocol? c) Is the principal investigator effectively and appropriately monitoring the progress of the study? d) How is the quality of the study: whether the study personnel, study centers, and data trial centers adhere to the requirements of SOPs? e) Are the data copied onto the Case Report Form (CRF) consistent with the original data? f) Overall trial quality (identifying the root causes of issues). g) Are study documents present? Are they stored systematically? Are they interpretable (can trial data be reconstructed from study documents)? h) Inspection of monitoring reports attempts to identify quality trends and consult on corrective measures for procedural issues that

 have arisen.

13) Regular inspections, preparation of inspection reports, and holding meetings with relevant personnel to discuss issues identified during the inspection.

2 Monitoring Plan

The monitor conducts three types of visits: study initiation visits, routine visits, and close-out visits.

2.1 Study Initiation Visits

Meet with the principal investigator, establish a visit plan, and introduce the monitoring objectives and plans to the investigator. Review includes: training manuals, forms, study protocols, qualifications of participating researchers, and compliance with data management SOPs, etc. If necessary, a start-up meeting can be convened to discuss the protocol and work content with all doctors and other staff participating in the study, clarify each person's responsibilities, explain the SOP requirements for data entry standards, and the preservation of original data.

2.2 Routine Visits

- ① Before each visit, review the progress of the trial and unresolved issues from previous visits, contact the investigator to confirm the visit date, develop a plan and agenda for this visit, prepare the required documents and items for the visit.
- ② Meet with the investigator to explain the main tasks of this visit, understand the progress of the trial (subject enrollment status, CRF completion status, informed consent signing status, etc.), and the resolution of problems identified during previous visits.
- ③ Check and update the investigator's management files, verify the original documents and CRF forms (pay attention to compliance, completeness, consistency with the protocol, discovery, and reporting of SAEs), check trial materials (storage conditions, distribution and recovery records, compliance with protocol requirements).
- ④ Collect CRF forms.
- (5) Record any issues discovered, discuss and resolve the problems identified during this visit with the investigator, exchange progress and experiences with other research units.
- 6 Store items retrieved, signed informed consent forms, CRF forms, etc., as required.
- ⑦ Complete the visit report, update various records, track and resolve any issues discovered, and schedule follow-up visit plans.
- ③ SAEs that occur during the clinical trial must be reported to the Ethics Committee within 24 hours.
- (9) Any changes to the protocol, CRF forms, etc., during the trial require approval from the Ethics Committee. Documents to be submitted to the Ethics Committee during the trial include: protocol amendments, informed consent form amendments, SAE reports, recruitment advertisements (if used).

2.3 Close-Out Visits

- 1 Review any outstanding issues from routine visits and confirm their resolution.
- 2 Confirm the visit time, develop a plan and agenda for this visit.
- 3 Confirm the completeness and updating of the investigator's management files.

- ④ Confirm that all CRF forms have been collected.
- ⁽⁵⁾ Confirm the reporting and tracking of SAEs.
- (6) Check the records of the transport, distribution, and retrieval of various materials for the study.

 \bigcirc Discuss and summarize, confirm any outstanding issues and follow-up work, explain the requirements for the preservation of trial-related documents.

(8) Follow-up work: Complete the trial close-out monitoring visit report, notify the Ethics Committee of the trial's conclusion, continue to track and resolve any outstanding issues, and archive all documents. Documents to be submitted to the Ethics Committee after the trial ends include: trial closure letter, SAEs after trial closure.

3 Data Requirements

Protocol: After careful reading and agreement, the principal investigator must sign and strictly adhere to the protocol implementation.

Clinical Trial Data: All various original clinical trial data should be recorded promptly, truthfully, accurately, and completely, and copies of laboratory test reports should be retained. The principal investigator must retain records and documents of the study implementation process, including eCRFs, informed consent forms, laboratory test results, and radiotherapy plans, for 5 years after the completion or termination of the study, or for a longer period as required by regulatory authorities (whichever is longer). After this time period, the documents may be destroyed in accordance with local regulatory requirements.

4 Study Summary

Once the required total number of cases is reached and verified, the data analysis center performs data analysis. Based on the statistical analysis report, the responsible unit of the clinical trial and participating units write a summary of the clinical trial and sub-center summary table according to the principles of Good Clinical Practice (GCP) clinical trial guidance.

5 Research Funding

The RecurIndex-related testing expenses for this trial are provided by the collaborating party, with specific funding arrangements outlined in a signed contract.

6 Financial Transparency

The principal investigator is required to provide complete and accurate financial information in accordance with Chinese regulations, in order to submit comprehensive and accurate financial statements or disclosure statements to relevant health authorities. The principal investigator is responsible for providing financial information from the beginning to the completion of the study period.

BMJ Open



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description
Administrative in	format	tion
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ($pg3$. <i>line 3</i>)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (<i>pg4. line 44)</i>
	2b	All items from the World Health Organization Trial Registration Data Set (Supplemental 14)
Protocol version	3	Date and version identifier (pg4. line 42)
Funding	4	Sources and types of financial, material, and other support ($pg14$. line 43)
Roles and	5a	Names, affiliations, and roles of protocol contributors (pg3. line 9)
responsibilities	5b	Name and contact information for the trial sponsor (pg3. line 54)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. ($pg14$. <i>line 33</i>)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (<i>pg4. line 60</i>)
	6b	Explanation for choice of comparators ($pg5$. line 20-43)
Objectives	7	Specific objectives or hypotheses (<i>pg8. line 14</i>)

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ($pg4$. line 26)
Methods: Partici	pants,	interventions, and outcomes
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (<i>pg6. line 59</i>)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ($pg7$. line 7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (<i>pg7. line 17 and pg9. line 52</i>)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ($pg10$. line 43)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ($pg7$. <i>line 52</i>)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Not available)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (<i>pg8. line 19</i>)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Table 3)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (<i>pg11. line 41</i>)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ($pg7$. <i>line 52</i>)
Methods: Assigr	nment	of interventions (for controlled trials)
Allocation:		

1 2 3 4 5 6 7 8 9	Sequence generation	16a	Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (<i>pg7. line 41</i>)
10 11 12 13 14	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned ($pg7$. <i>line 45</i>)
15 16 17	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ($pg7$. <i>line 52</i>)
19 20 21 22	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (Not applicable)
23 24 25 26		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (Not applicable)
27 28	Methods: Data co	llectio	n, management, and analysis
29 30 31 32 33 34 35 36 37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (<i>pg11. line 20</i>)
38 39 40 41		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ($pg10$. line 40)
42 43 44 45 46 47 48	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (<i>pg11</i> . <i>line 22</i>)
49 50 51 52	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (Supplementary 15)
55 56		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (Supplementary 15)
57 58 59 60		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (Supplementay15)

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Methods: Monito	ring	
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Supplementary 16)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (Supplementary 15)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Supplementary 15)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Supplementary 16)
Ethics and disse	minati	on
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ($pg12$. <i>line 35</i>)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (<i>pg12. line 45</i>)
Consent or assent	t 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ($pg12$. line 48)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ($pg14$. <i>line</i> 51)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Supplementary 16)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (<i>pg4. line 44</i>)
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ("Informed Consent Form for RCT" and "Informed Consent Form for Tumor Tissue Biopsy")
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (Supplementary 17)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.

Author notes: the above pages and line numbers refer to the first submission synthesized PDF, titled *bmjopen-2023-078049_Proof_hi*.

RecurIndex-Guided postoperative radiotherapy with or without Avoidance of Irradiation of regional Nodes in 1-3 node-positive breast cancer (RIGAIN): a study protocol for a multicenter, open-label, randomized controlled prospective phase III trial

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	Secondary Subject Heading:	Oncology, Evidence based practice	
	Keywords:	RADIOTHERAPY, Breast tumours < ONCOLOGY, Oncogenes < ONCOLOGY	
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<u>RecurIndex-Guided</u> postoperative radiotherapy with or without <u>A</u>voidance of <u>I</u>rradiation of regional <u>N</u>odes in 1-3 node-positive breast cancer (RIGAIN): a study protocol for a multicenter, open-label, randomized controlled prospective phase III trial

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ABSTRACT

Introduction

Postoperative radiotherapy in breast cancer patients with 1-3 lymph node metastases, particularly within the pT1-2N1M0 cohort with a low clinical risk of local-regional recurrence (LRR), has incited a discourse surrounding personalized treatment strategies. Multigene testing for Recurrence Index (RI) model capably differentiates patients based on their level of LRR risk. This research aims to validate whether a more aggressive treatment approach can enhance clinical outcomes in N1 patients who possess a clinically low risk of LRR, yet a high RecurIndex-determined risk of LRR. Specifically, this entails postoperative whole breast irradiation (WBI) combined with regional lymph node irradiation (RNI) following breast-conserving surgery (BCS) or chest wall irradiation (CWI) with RNI after mastectomy.

Methods and Analysis

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. In this study, patients with low clinical LRR risk but high RecurIndex LRR risk are randomly assigned in a 1:1 ratio to the experimental group or the control group. In the experimental group, RNI is performed and the control group omits RNI. Efficacy and safety analyses will be conducted, enrolling a total of 540 patients (270 per group). The primary endpoint is invasive disease-free survival, and secondary endpoints include any first recurrence, local-regional recurrence-free survival, distant metastasis-free survival, recurrence-free survival, overall survival, disease-free survival, breast cancer-specific mortality, and assessment of patient quality of life. The study began in April 2023 and with a follow-up period of 60 months after the last participant completes radiation therapy.

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Ethics and dissemination

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yatsen University (SYSKY-2022-097-02, version 3.1). It adheres to the Helsinki Declaration and good clinical practice. Research findings will be submitted for publication in peer-reviewed journals.

Trial registration number NCT04069884

STRENGTHS AND LIMITATIONS OF THIS STUDY

- > The trial is designed as a multicenter, open -label, randomized, controlled phase III study.
- > Introduced a multigene model to guide precision radiotherapy.
- > This research utilizes IDFS as the primary endpoint.
- > The trial is conducted only in one country (China).

INTRODUCTION

Patients with 1-3 axillary lymph node metastases constitute approximately 25 to 30% of early operable breast cancer cases. Radiotherapy plays a pivotal role in the comprehensive treatment of

breast cancer^{1,2}. However, the benefit of postoperative radiotherapy for N1 breast cancer patients, particularly in terms of survival improvement, remains a topic of substantial debate. Studies conducted in the 1990s such as the Vancouver study, DBCG-82b/82c, and the early meta-analysis by EBCTCG (including the N1 subgroup) consistently demonstrated that postoperative radiotherapy significantly enhances disease-free survival (DFS) and overall survival (OS) for patients³⁻⁷. Consequently, N1 becomes a relative indication for postoperative radiotherapy. The 2011/2014 EBCTCG meta-analysis further suggested that postoperative radiotherapy could convert a 1.5% reduction in the 10-year any first recurrence rate (AFRR) into a 1% 20-year OS benefit^{8,9}. The MA20 and EORTC 22922 studies published in 2015^{10,11}, which

focused on T1-2N1 patients, especially those with high clinical risk of LRR and compared

postoperative RNI after BCS or without RNI, found that more aggressive postoperative RNI for T1-2N1 patients could result in better distant metastases-free survival (DMFS), DFS, or breast cancer-specific mortality (BCSM). The Vancouver study's 20-year long-term follow-up results demonstrated the long-term OS benefit of postoperative radiotherapy in the N1 subgroup. These milestone studies further reinforced the value and recommendation of postoperative radiotherapy for N1 breast cancer patients, rendering N1 staging a strong relative indication for postoperative radiotherapy and increasing the number of patients actively accepting postoperative radiotherapy. Nevertheless, not all N1 patients will benefit from postoperative radiotherapy. Some real-world retrospective studies reveal limited LRR and/or survival improvement from postoperative radiotherapy, particularly RNI therapy, among certain N1 patients, especially those with relatively low clinical risk. Consequently, the necessity of radiotherapy for clinically low LRR risk N1 patients remains a topic of significant controversy and uncertainty. Clinical practice often presents varying professional recommendations for postoperative radiotherapy in low-risk N1 patients, resulting in the exclusion of a substantial number of patients solely based on traditional clinical and pathological features. However, this omission of RNI could lead to inadequate treatment, with potential implications for tumor recurrence, metastasis, and patient survival. Conversely, a uniform approach of postoperative radiotherapy for all clinically low LRR risk N1 patients would inevitably result in overtreatment and expose patients to additional risks such as radiation-induced injury and related complications, thereby impacting their quality of life¹²⁻¹⁵.

When considering low-risk N1 breast cancer patients, then, the primary objective is to identify the actual high-risk patients concealed within the clinically low-risk population and to strategically administer postoperative radiotherapy. This represents one of the essential development directions of early breast cancer "precision radiotherapy" in the future. Achieving individualized and precise radiotherapy depends on the discovery of molecular genetic prediction models that can accurately predict local-regional recurrence risk in a scientific, reliable, and accessible manner. Currently approved multi-gene detection models abroad include Oncotype DX, MammaPrint, and EndoPredict. Oncotype DX is the most representative and extensively utilized multi-gene prognostic analysis method, primarily employed to guide early luminal low-risk patients to avoid adjuvant chemotherapy. Oncotype DX is currently more frequently used in the radiotherapy field to identify low-risk elderly N0 breast-conserving patients exempt from postoperative radiotherapy. Although the predictive value in the N1 population has initially

demonstrated some clinical significance, contradictions exist between various research findings¹⁶⁻¹⁹. No prospective high-level evidence for multi-gene models predicting RNI benefits in N1 patients is currently available. The clinical trial Tailor RT (MA 39) conducted by the Canadian Cancer Trials Group primarily investigates whether low-risk recurrence patients can be spared from postoperative radiotherapy or RNI. This is currently the only prospective, randomized, controlled phase III study internationally that utilizes a multi-gene predictive model to guide precise radiotherapy for N1 patients. The future research outcomes will primarily be applied to guide the omission of postoperative radiotherapy in clinically low LRR risk and genetically low-risk N1 patients. However, the significance of postoperative radiotherapy for patients with intersecting risks, especially those with clinically low-risk but genetically high-risk profiles, remains uncertain.

RecurIndex is the only risk prediction model developed based on the Chinese population for early-stage breast cancer. Consisting of 18 core genes and 10 IHC4 reference genes, it is capable of independently predicting the risk of LRR and distant metastasis²⁰⁻²⁴. Internal validation studies in Taiwan and external validation studies conducted in Singapore, Hong Kong, and the Fourth Affiliated Hospital of Hebei Medical University in China have all provided strong evidence of RecurIndex's predictive efficacy and its value in guiding radiotherapy for N1 patients^{25,26}. Lowrisk and high-risk patients identified by RI-LRR had 5-year LRR rates of 0% and 7%, respectively (P=0.0146). Compared to high-risk RI-LRR patients who did not receive postoperative radiotherapy, those who underwent postoperative radiotherapy demonstrated significantly improved rates of LRR and RFS, with percentages of 88.8% vs 74.1% (P=0.0071) and 79.4% vs 59.5% (P=0.0019), respectively. These results clearly indicate the significant benefits of postoperative radiotherapy in this patient population. To date, RecurIndex has become widely recognized and clinically implemented around the Asia-Pacific region. It has been incorporated into the "Expert Consensus on Multigene Testing for Adjuvant Therapy of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer" in China and recommended in the "Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Breast Cancer 2022" for guiding precise postoperative radiotherapy in N1 patients. However, further high-level, randomized, controlled phase III clinical trials are needed to validate its clinical applications and expand its usage in the field. The most promising and crucial area for its application lies in guiding precise radiotherapy for N1 breast cancer patients.

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In summary, we have begun conducting a multicenter, prospective, randomized, controlled phase III clinical study of individualized precision radiotherapy for clinically low LRR risk breast cancer patients with N1 guided by RecurIndex. This study aims to evaluate patients' local recurrence and distant metastasis risks, primarily investigating whether active postoperative radiotherapy can further improve clinical efficacy in N1 patients with clinically low risk but high RecurIndex LRR risk. The ultimate goal of this study is to provide high-level clinical evidence and reliable multi-gene recurrence risk prediction models to help achieve individualized precision radiotherapy for N1 breast cancer patients.

MATERIALS AND METHODS

The RIGAIN study is a multicenter, prospective, randomized, open-label, phase III clinical trial that is being conducted in China. The overall research process is illustrated in Figure 1. This study aims to screen postoperative patients with early-stage breast cancer (pT1-2N1M0) who have completed standard systemic therapy and possess eligible pathological specimens for participation. The inclusion and exclusion criteria are listed in Table 1. RecurIndex testing will be performed using postoperative paraffin-embedded tissue sections from the primary lesion. The study is divided into a randomized controlled trial and an observational study based on clinical risk and RecurIndex LRR risk. Patients with low clinical risk but high RecurIndex LRR risk will be randomly assigned in a 1:1 ratio to either the experimental group (RNI) or the control group (No RNI), while patients with low clinical risk and low RecurIndex LRR risk will be included in the observational study. This article primarily focuses on the randomized controlled trial. The study participants will receive the following treatments. Experimental group: For patients who underwent BCS, RNI will be performed in combination with whole breast irradiation (WBI) + tumor bed boost irradiation. For patients who underwent mastectomy, chest wall irradiation (CWI) will be administered in combination with RNI. Control group: RNI will be omitted. For patients who underwent BCS, only WBI + tumor bed boost irradiation will be administered. For patients who underwent mastectomy, both RNI and CWI will be omitted. A comparative effectiveness analysis will be conducted. The study commenced in April 2023.

Randomization Method

Stratified randomization will be used for the randomized study. For the active postoperative radiotherapy trial involving the clinically low LRR risk but high RecurIndex LRR risk population, participants will be stratified by N1 status, surgical method, and enrolling hospital, and then randomized in a 1:1 ratio into the experimental and control groups.

Randomization stratification factors are as follows:

- a) N1 status: N1mic or 1-2 LN macrometastasis (including N1sln), or 3 LN macrometastasis;
- b) Surgical method: breast-conserving surgery or mastectomy; and
- c) Multicenter enrolling hospital.

A central randomization system was developed by TaiMei Medical Technology Company to facilitate the randomization process. Statistical experts responsible for randomization designed the randomization parameters in advance, allowing the system to generate a random allocation table. The main clinical trial centers conduct eligibility screening for potential participants. Once deemed eligible, the researchers at each sub-center access the server via the internet and enter the information of the enrolled patients. The system then assigns a corresponding randomization number based on the random allocation table, determining the patient's placement in the respective study group.

Participants and recruitment

Patients will be recruited by radiation oncologists from each participating research center. For each interested patient, the clinician or clinical coordinator will provide a complete and comprehensive introduction to them or their designated representative, informing the patient about their rights, the risks involved, and the potential benefits they may receive to enhance their Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

compliance with the protocol. Prior to enrollment, patients are required to sign an informed consent form, which will be kept in the Case Report Form (CRF). Patient registration is scheduled to begin on April 1, 2023 (See supplementary 1 for details), and is expected to continue for 5 years (tentatively until January 2028). The final collection of data for the primary outcome measures is anticipated to be completed by December 2032.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Objectives and endpoints

This study aims to evaluate whether adjuvant radiotherapy to the regional lymph nodes after breast-conserving surgery or chest wall plus regional lymph node radiotherapy after total mastectomy can further improve clinical outcomes in N1 patients with low clinical risk but high RecurIndex LRR risk.

The primary endpoint is invasive disease-free survival (IDFS). Secondary endpoints are any first recurrence (AFR), local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), recurrence-free survival (RFS), overall Survival (OS), disease-free survival (DFS), breast cancer-specific mortality (BCSM) and patient quality of life assessment. The specific definitions can be found in Table 2.

During the screening period and 3 months after the end of treatment, patients in each group fill out the quality of life questionnaire (EORTC QLQ-C30), as well as the breast cancer survival quality scale (EORTC QLQ-BS23) annually during the follow-up phase. (Supplementary 2 and 3).

RecurIndex Test

RecurIndex testing was performed using postoperative paraffin-embedded tissue sections from the primary lesion of the subjects. All sections were uniformly sent to the Jiangsu Simcere Pharmaceutical Co., Ltd., Jiangsu Simcere Diagnostics Co. for free testing, Ltd. Formalin-fixed, paraffin-embedded tissue blocks should be selected that cover the largest amount of tumor cells and meet the diagnostic criteria in appearance. Tissue sections with an excess amount of normal tissue, necrotic tissue, adipose tissue, or hemorrhagic tissue should not be sent for examination. The tumor cell content in the identified sections should be >50% for the test to be performed. A total of 10 consecutive sections are needed, each with a thickness of 5 microns. The sections can remain unstained and without coverslips. There is no need to oven-dry the sections; they can be air-dried naturally.

Safety Assessment Indicators

All patients participating in the RIGAIN study are required to undergo safety assessments, including acute radiation reactions and late radiation injuries for radiotherapy patients. The evaluation criteria and handling of injuries are detailed in Supplementary 4-7. Their treatment is shown in Supplementary 8. Including acute skin reactions to radiotherapy, symptomatic radiation pneumonitis, long-term cosmetic outcomes (BCS/reconstruction patients), skin fibrosis (total mastectomy patients), ischemic heart disease, upper limb edema^{27,28}, brachial plexus injury and
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second primary tumor²⁹.

Radiotherapy

General consideration

The overall treatment plan for each participant is determined by the researchers at the corresponding sub-center based on the participant's condition. Depending on their assigned group, patients will either undergo RNI or be exempted from it. Breast-conserving patients will all receive WBI. Patients should start radiotherapy within 8 weeks after completion of adjuvant chemotherapy. The regional lymph nodes include the supraclavicular lymph nodes and infraclavicular lymph nodes (unresected levels II/III axillary lymph nodes), with or without internal mammary lymph nodes (at least from the 1st to the 3rd intercostal space). For patients with minimally positive SLN and without ALND, the inclusion criteria encompass the low/intermediate axillary lymph nodes. The planned endocrine therapy and anti-HER2 treatment can be continued during the RT process.

Patient positioning and immobilization

The patient lies on a fixed device such as a breast support, vacuum bag, or foam pad. A CT scan is performed with a thickness of 3-5 mm, from the second cervical vertebra to the second lumbar vertebra. CT positioning includes surface marking, where lead wires are placed on the surgical scar of the primary lesion in breast-conserving patients or the chest wall scar in total mastectomy patients, as well as on the scar of the axillary sentinel/clearance lymph node incision. If there is a drainage site, it should also be separately marked with a lead wire or lead point.

Volumes of interest

The clinical target volume (CTV) and organs at risk (OAR) must be delineated on all CT slices, following the contouring guidelines of the Radiation Therapy Oncology Group (RTOG) and considering the actual situation at each CT slice. Detailed descriptions of CTV and OARs can be found in Supplementary 9. The margin between the planning target volume (PTV) and CTV depends on the institutional standards of each participating center, with a recommended minimum of 5 mm. Contours should be drawn according to the RTOG guidelines, including the ipsilateral and contralateral lungs, heart, humeral heads, and spinal cord.

External beam equipment and techniques

Radiation therapy techniques that can be employed include three-dimensional conformal radiotherapy (3DCRT), forward intensity-modulated radiotherapy (F-IMRT), inward intensity-modulated radiotherapy (I-IMRT), volumetric modulated arc therapy (VMAT), and helical tomotherapy (HT). Conventional radiotherapy (using a simulator for positioning and a 2D planning system to design treatment plans with external and tangential fields) and proton therapy techniques are not allowed. Some variations in treatment planning and implementation are permitted to accommodate the participating centers in adapting to the research protocol. However, it is strongly recommended that the treatment plans for enrolled patients at each center remain consistent to avoid confusion.

Dose prescription, fractionation

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The whole breast target volume, or the integrated target volume of the whole breast and low to moderate axillary region, or the chest wall target volume, and the regional lymph node target volume receive a radiation dose of 5000 cGy in 25 fractions, delivered at a rate of 200 cGy per day, five days per week. Alternatively, a hypofractionated radiotherapy scheme can be chosen, with a radiation dose of 4000-4256 cGy in 15 to 16 fractions. For breast-conserving patients, a sequential tumor bed boost is performed after completion of whole breast irradiation, as determined by individual center investigators. It can be delivered using conventional fractionation, with a dose of 798 cGy-1064 cGy in 3 to 4 fractions at a rate of 266 cGy per day. If there are high-risk factors for local recurrence, such as positive surgical margins, close margins, or young age, the radiation dose for the tumor bed boost may be increased to 1400-1600 cGy in 7 to 8 fractions at a rate of 200 cGy per day (See supplementary 10 for details).

DVH constraints

It is required that at least 95% of the prescribed dose to the PTV covers 95% of the PTV. The specific dose distribution is determined by each center's policy, with a recommended level as shown in Supplementary 11. For breast-conserving patients, it is recommended to achieve a central axis dose uniformity of $\leq \pm 7\%$ for PTV_2 (whole breast or integrated target volume of whole breast and low to moderate axillary region) and PTV_1 (tumor bed), and to minimize the volume receiving $\geq 105\%$ of the prescribed dose. The constraints for organs at risk should follow the Quantitative Analysis of Normal Tissue Effects in Clinical (QUANTEC) guidelines (see Supplementary 12).

Withdrawal from research and study termination

Termination of treatment

Research treatment will be terminated if any of the following conditions occur in the patient. The following are the criteria for the withdrawal or dropout of subjects:

- 1. The subject withdraws informed consent;
- 2. Any AE causes the subject to be unable to continue participating in the study;
- 3. The subject is lost to follow-up;
- 4. The subject does not comply with the study requirements and/or the investigator's instructions;
- 5. The subject has a concomitant illness or change in the subject's condition, and the investigator believes the subject is no longer suitable for the study treatment; or
- 6. For any other reason the investigator believes the subject is not suitable for continuing in the study.
- 7. If a subject drops out or withdraws, relevant safety and efficacy evaluations should be completed as soon as possible.

Study Termination

The trial will be terminated if any of the following situations occur during the trial:

- 1. Serious safety issues arise during the trial;
- 2. There is a major error in the study protocol;
- 3. The principal investigator voluntarily stops the trial; or
- 4. The administrative authority revokes the trial.

5. The termination of the trial may be temporary or permanent.

If the trial is terminated, all trial records should be retained for review.

Follow-up evaluation and toxicity assessment

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The registration timeline, intervention measures, and assessments are presented in Supplementary 13. In the follow-up phase after radiotherapy, check-ups and assessments will be performed every six months until the occurrence of an endpoint event or the end of the study. For patients without postoperative radiotherapy, check-ups and assessments will be conducted every six months after the completion of adjuvant chemotherapy until the occurrence of an endpoint event or the end of the study. Effectiveness evaluations include tumor imaging examinations and assessments, brain MRI or CT, bone scans, quality of life questionnaires (EORTC QLQ-C30), and breast cancer-specific quality of life scales (EORTC QLQ-BS23). Safety evaluations include but are not limited to physical examinations, ECOG PS scores, pregnancy test checks, blood routine tests, blood biochemistry tests, adverse events, and serious adverse events. At the end of the study, participants will undergo physical examinations, performance status assessments (ECOG PS), blood routine tests, blood biochemistry tests, tumor markers, breast ultrasound/MRI, mammography, chest X-ray/CT, abdominal ultrasound/CT, and EORTC QLQ-C30 and EORTC QLQ-BS23 scoring. Evaluations of concomitant medications and adverse events are also required. The end-of-study visit window is 60 months after the last participant completes radiotherapy. For participants who are withdrawn or drop out before the end of the study, safety and effectiveness assessments will be conducted according to the requirements of end-of-study safety and effectiveness visits.

Data Management and Quality Assurance

In this study, electronic case report forms (eCRF) are used to collect data, and the EDC system designated by the principal investigator is used to complete the eCRF. Monitors verify the original data to ensure that the data entered into the eCRF by authorized trial center personnel (i.e., original data) is accurate, complete, and derived from original documents. Researchers and trial institutions must provide monitors with direct access to applicable source documents and reports for inspection and IEB/EC review (See supplementary 14 for details). A Data Safety Committee has also been established, consisting of 5 members who are independent of the project team and have signed a research confidentiality agreement. The main tasks of the committee are to review and analyze positive results (recurrence and metastasis of subjects) and to understand the actual research results (without statistical analysis) when half of the subjects are enrolled. The committee will vote on whether it is necessary to adjust the research plan. This protocol does not include investigational drugs, and any toxicities that occur during treatment should be reported to the principal investigator and their ethics committee. In addition, the subcenters should also report to the ethics committee of their institution. All serious adverse events and other adverse events must be recorded in the case report form. Furthermore, we have established a comprehensive Quality Control Standard Operating Procedure (SOP), as detailed in Supplementary 15.

Sample Size Estimation

This study is designed for superiority, referring to authoritative postoperative radiotherapy studies MA20¹⁰ and EROTC22922¹¹ for N1 patients, in which the 5-year IDFS in the

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radiotherapy group and the control group were 90.7% vs 81.9% and 87.7% vs 77.1%, respectively. In the domestic RecurIndex external validation retrospective study²¹ for N1 breast cancer patients, the 5-year IDFS in the high RI-LRR risk group was 81.1% vs 69.7% in the postoperative radiotherapy group and the control group, respectively. It is expected that the 5-year IDFS for the clinically low LRR risk and high RecurIndex LRR risk population in the experimental group and control group in this study will be 89% and 82%, respectively. The superiority margin is set to improve the primary endpoint IDFS by \geq 7% (HR=0.587) in the postoperative radiotherapy research group compared to the control group. With a one-sided significance level (α) of 0.025 and a power (1- β) of 0.8, assuming the experimental group performs better than the control group, the required sample size for each group was calculated as 216 cases per group using PASS15.0 software. The allocation ratio between the experimental and control groups was set at 1:1. Considering a 5-year enrollment period, 5-year follow-up period, and potential 20% dropout rate (mainly considering the need for further 10-year and 15-year long-term efficacy follow-up after reaching the 5-year endpoint), each group will need 270 cases, totaling 540 cases.

Statistical analysis

Descriptive statistical analyses will be conducted based on demographic characteristics such as age, gender, height, weight, and other baseline characteristics such as medical history. The Cox proportional-hazards model will be used for analysis of the primary endpoint. The Hazards Ratio and its 95% confidence interval will be calculated, including stratification factors and other covariates. Additionally, the Cox proportional-hazards model without covariates will be used to support the analysis results of the primary endpoint. Moreover, the Kaplan-Meier (KM) method will be used to calculate the median invasive disease-free survival for the two groups (experimental group vs control group), including 95% confidence intervals. KM plots will be used to illustrate the time trends of IDFS. For the secondary endpoints, the AFR of each group will be calculated, as well as the corresponding 95% Clopper-Pearson confidence intervals. LRFS, DMFS, RFS, OS, DFS, and BCSM will be analyzed for median values using the KM method (including 95% confidence intervals). The overall changes in EORTC QLQ-C30 and EORTC QLQ-BS23 scores from baseline will be summarized. Safety analysis will be conducted by summarizing adverse events, changes in laboratory test results, changes in vital signs, and study treatment exposure. The results will be reported by treatment group. All adverse events during treatment, grade 3 or higher TEAEs, serious adverse events (SAEs), radiotherapy-related SAEs, and TEAEs leading to study termination will be summarized by organ system, preferred term, and group in terms of numbers and percentages (See supplementary 16 for details). A p value ≤0.05 in a two-tailed test will be considered statistically significant. Statistical analyses will be performed using SPSS V.25.0 (Statistical Package for Social Sciences) and STATA V.14.

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Ethics and dissemination

This study has obtained approval from the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2022-097-02, version 3.1), as well as approval from the respective participating centers' ethics committees. The study is being conducted in accordance with the Helsinki Declaration and good clinical practice. Approval from the Chinese Human Genetic Resources Office was obtained on January 6, 2021, with the reference number 2020SQCJ2358. The study was registered on ClinicalTrials.gov on July 7, 2022, with the registration number NCT04069884. The research findings will be published in peer-reviewed journals. The authors will be individuals who have made significant contributions to the study, design, and implementation. Any modifications to the study protocol and informed consent documents must be reviewed and approved by the Ethics Committee before implementation.

Confidentiality and protection of participants' rights and interests

Researchers are required to explain to participants that participation in the clinical trial is voluntary, and that they have the right to withdraw from the study at any stage without affecting their medical treatment and rights. Personal information of participants will be kept confidential. Participants should be informed about the nature, purpose, potential benefits, and possible risks of the clinical trial, as well as alternative treatment options. Researchers should ensure that the rights and obligations of participants, as stipulated in the declaration, are protected. Participants should be given adequate time to consider whether to participate and to sign the informed consent form.

Discussion

The RIGAIN study is a multicenter, open-label, randomized controlled phase III clinical trial. Our objective is to precisely assess patients with clinically low LRR risk N1 breast cancer who, if identified as high-risk for LRR by the RecurIndex test, may receive enhanced clinical efficacy from active RNI after BCS or CWI with RNI after mastectomy. The aim is to accurately identify patients who would benefit from intensified radiotherapy. In addition, we have established an observational study to investigate the potential to exclude RNI for patients who are clinically low LRR risk and are identified as low risk for LRR by the RecurIndex. The primary endpoint of the study is LRR, with the aim of identifying truly low-risk patients for whom radiotherapy can be safely omitted from planned treatment regimens. Similarly, the MA39 study defines a clinically and genetically low-risk LRR N1 population (age \geq 40 years, luminal A type, Oncotype DX score <18) based on comprehensive clinical pathology, molecular subtype, and a multigene model. The anticipated results from the MA39 study could potentially guide personalized RNI decisions for patients who are found to be both clinically and genetically low risk. However, this study also has limitations. Firstly, the multi-gene models used in this study were developed to predict the risk of distant metastasis, and there may be inconsistencies between the occurrence of LRR and the risk of distant metastasis in clinical patients. Secondly, future research results are primarily intended to guide the omission of postoperative radiotherapy in clinically low-risk and genomically low-risk N1 patients. However, the significance of postoperative radiotherapy in patients with intersecting risks, particularly those who are clinically low-risk but genomically high-risk, remains unclear. Lastly, this study does not provide direct evidence for the application of Oncotype DX in guiding treatment decisions for Asian patients.

Traditionally, postoperative radiotherapy has been lauded for decreasing LRR and for helping to diminish the risk of distant metastases^{10,11}. This has lead to long-term improvements in DFS and BCSS, providing the ultimate benefit to patients. Notably, this is partly attributed to the prevention of reseeding from recurrences. Another part is attributed to the radiation-induced

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abscopal killing effect (RIAKE), which refers to a series of immunological responses induced by local high-dose radiotherapy that culminate in the elimination of tumors distant from the irradiation site²⁷. In the context of postoperative radiotherapy for patients with regionally lymph node-positive breast cancer, the abscopal effect is most pronounced in patients classified as pN1, where the survival benefit is most conspicuous⁹. Compared to mastectomy, BCS better preserves the immune microenvironment, thereby enhancing the transformation and activation of the immune response following postoperative radiotherapy. This is the primary reason for our selection of IDFS as the main endpoint in this study.

Oncotype DX and MammaPrint assays primarily assess the overall recurrence risk and mainly guide chemotherapy and endocrine treatment^{16,18,30}. Previous studies have indicated a high concordance in predicting the risk of distant metastases between the RecurIndex and the MammaPrint and Oncotype DX assays. However, some discrepancies exist in assessing the risk of LRR. The TAILORx study indicated that the RecurIndex predictive model may identify patients at risk of locoregional recurrence more accurately than the Oncotype DX^{16,31,32}.

The RecurIndex predictive model stands out amongst various multigene prediction models in early-stage breast cancer with the following unique characteristics and advantages: 1. Unlike other models that only assess overall recurrence risk and are more biased towards the risk of distant metastases, RecurIndex can independently assess both the risk of locoregional recurrence and distant metastases, making it more suitable to guide precision radiotherapy; 2. RecurIndex demonstrates predictive efficacy in populations with HER2 overexpression and triple-negative breast cancer, potentially serving as a precise predictor of locoregional recurrence risk in patients with these two types of N1mic tumors, which could help guide individualized radiotherapy decisions.

The study focuses on the RecurIndex risk prediction model with the aim of guiding postoperative individualized radiotherapy for pT1-2N1M0 breast cancer patients. Particular attention is paid to the "clinically low LRR risk" but "genetically high-risk" population to explore and validate the clinical benefits of postoperative radiotherapy. The study design stands out for its clinical applicability and innovation as well as strict adherence to ethical and clinical practice standards. It effectively addresses the research gap in precise radiotherapy for N1 patients with overlapping risk profiles, both domestically and internationally. The study could potentially revolutionize the practice of postoperative radiotherapy by transitioning from a discretionary approach solely based on clinical and pathological information to an individualized optimization guided by clinical-genetic risk.

We anticipate that the RIGAIN study will generate high-quality evidence, establishing a precise risk assessment framework to guide optimized radiotherapy decisions for N1 breast cancer patients.

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Contributors

XH, YT and ZB designed the original protocol for the study. JC contributed to study management. JL, XH, YT and ZB drafted the manuscript. JL submitted the study. YT and ZB performed the sample size calculation and data analysis. RD and FW offer genetic testing. XH, JL, YT, JC, SH, AZ, LZ, YW, ZL, HY, XX, JC, XW-L, XL, XZ, WZ and XY participated in enrollment, treatment and follow-up of patients.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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	clusion criteria
1.	Age ≥ 18 years, ≤ 70 years;
2.	ECOG PS ≤ 2 (Supplementary 17);
3.	Postoperative pathology confirms the diagnosis of invasive breast cancer;
4.	Meets the clinical definition of low risk: (1) Axillary lymph node micrometa
(N	1mic), or (2) N1 patients who meet all of the following conditions: a) Age \geq 40 year
Ly	mphovascular invasion (LVI) negative or limited to individual or small foci of
(e	cluding extensive or large amounts of LVI); c) Three clinical molecular subtypes (Lu
А	type, Luminal B1 type, and Luminal B2 type) are allowed in this study: ER-po
(E	$R \ge 1\%$) and HER2-negative, or ER-positive (ER $\ge 1\%$) and HER2 overexpress
re	pectively.
5.	Postoperative pathological diagnosis of axillary lymph node status as any of the follow
a.	Sentinel lymph node biopsy or axillary lymph node dissection with micrometastasis (N1
b.	Sentinel lymph node biopsy with 1-2 lymph node macrometastasis (N1sln), c. Sen
ly	nph node biopsy + axillary lymph node dissection or simple axillary lymph node disse
W	th 1-3 lymph node metastasis (N1);
6.	The primary tumor and breast underwent breast-conserving surgery or mastector
br	east reconstruction (autologous/prosthetic);
/.	A thorough systemic examination (e.g., chest X-ray, ultrasound, C1, etc.) within 3 me
be	fore randomization for radiotherapy must confirm no distant metastasis;
8.	Mammography and/or MRI within 12 months before surgery or randomization
ra	notherapy must confirm no contralateral breast cancer;
9.	Postoperative completion of at least 4 cycles of adjuvant chemotherapy conta
an 10	Radiotherany must be performed sequentially after the completion of all adj
ch	emotherapy starting no later than 8 weeks after the end of chemotherapy:
11	Patients must have sufficient postoperative paraffin tissue sections of the primary t
fo	RecurIndex testing.
12	No history of other malignant tumors except for basal cell carcinoma of the skin and
13	Signed informed consent before the start of the study
E	clusion criteria
1.	Confirmed T3-4, N0, N2-3, M1 stage disease before postoperative radiothe
en	rollment:
2.	Received any neoadjuvant treatment before surgery, including chemotherapy, endo
th	erapy, targeted therapy, or radiotherapy;
3.	Patients who underwent mastectomy and only had sentinel lymph node biopsy;
4.	History of contralateral breast cancer or other second primary malignant tumor (exclu
ba	sal cell carcinoma of the skin and cervical carcinoma in situ);
5.	Previous history of chest radiotherapy;
6.	Presence of severe heart, lung, liver, kidney, hematopoietic system, or nervous sy
di	seases, or mental disorders;
7.	Presence of scleroderma or active systemic lupus erythematosus or other autoimi
di	seases;
	Pregnant and breastfeeding patients.

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Table 2. The specific definitions of the study endpoints

IDFS	The time from the day the subject is randomized to the earliest occurrence of invasive
	cancer local recurrence, distant metastasis, or death, but does not include contralateral
	breast second primary cancer.
AFR	Any ipsilateral chest wall, breast, regional lymph node recurrence, or distant
	metastasis event that occurs during the follow-up period.
LRFS	The time from the day the subject is randomized to the earliest occurrence of
	ipsilateral chest wall, breast, or regional lymph node recurrence or death.
DMFS	The time from the day the subject is randomized to the earliest occurrence of distant
	metastasis or death.
RFS	The time from the day the subject is randomized to the earliest occurrence of
	ipsilateral chest wall, breast, regional lymph node recurrence, distant metastasis, or
00	
	The time from the day the subject is randomized until the patient's death.
DFS	The time from the day the subject is randomized to the recurrence of the disease or
DCSM	The time from the day the subject is rendemized to dooth from broost concern
BC2M	The time from the day the subject is randomized to death from breast cancer.



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Supplementary	1 Trial	ragistrat	ion data
Supplementary	1. Illai	registiat	ion uata

Data category	Information
Primary registry and trial identifying number	Line 44 page 4
Date of registration in primary registry	April 1. 2023
Source(s) of monetary or material support	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
Primary sponsor	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
Secondary sponsor(s)	the Jiangsu Simcere Pharmaceutical Co., Ltd., Jiangsu
	Simcere Diagnostics Co., Ltd
Contact for public queries	Xiaobo Huang, MD. [huangxbo@mail.sysu.edu.cn]
Contact for scientific queries	Xiaobo Huang, MD. Sun Yat-Sen Memorial Hospital, Sun
	Yat-Sen University, Guangzhou, Guangdong, China
Public title	RIGAIN Study
Scientific title	Line 3 page 3
Countries of recruitment	Line 29 page 4
Health condition(s) or problem(s) studied	Regional lymph node irradiation
Intervention(s)	Line 26 page 4
Key inclusion and exclusion criteria	Table 1 Line 3 page 18
Study type	Line 27 page 4
Date of first enrolment	Line 38 page 4
Target sample size	Line 33 page 4
Recruitment status	Recruiting
Primary outcome(s)	Line 19 page 8
Key secondary outcomes	Line 19 page 8

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3	Supplementary 2. Quality of Life Questionnaire EORTC OLO-C	C30 (r	version 3	5)	
4	We are interested in learning some information about you and your health status. Ple	ease an	swer all of	the follow	ing questions
5	independently and circle the answer that is most appropriate for you. There are no "c	correct'	' or "incorr	ect" answe	rs. The
7	information you provide will be kept strictly confidential		or meon	cot unove	15. 1110
8	Diago fill in your lost name:				
9	Dete chief (conserved des)				
10	Date of birth (year, month, day):				
12	Ioday's date (year, month, day):				
13		No	A little	Some	Very much
14	1.Do you feel difficulty when you do some laborious movements, such as lifting	1	2	3	4
15	heavy shopping bags or luggage?				
16 17	2. Do you find it difficult to walk long distances?	1	2	3	4
18	3. Do you find it difficult to walk short distances outdoors?	1	2	3	4
19	4. During the day, do you have to lie in bed or sit in a chair?	1	2	3	4
20	5. Do you need assistance with eating, dressing, washing or going to the	1	2	3	4
21	bathroom?				
22	In the past week:	1	2	3	4
24	6. Are your work or daily activities limited by physical ability?	1	2	3	4
25	7 Are your hobbies and leisure activities physically limited?	1	2	3	4
26	 P. De vou ever feel chort of breath? 	1	2	2	т Д
27		1	2	3	4
29	9. Have you ever had any pain?	1	2	3	4
30	10. Have you ever needed rest?	1	2	3	4
31	11. Have you ever felt sleep deprived?	1	2	3	4
32	12. Have you ever felt weak?	1	2	3	4
33 34	13. Have you ever felt a lack of appetite?	1	2	3	4
35	14. Have you ever felt nauseous and wanted to vomit?	1	2	3	4
36	15. Have you ever vomited?	1	2	3	4
37	16. Have you ever had constipation?	1	2	3	4
38	17. Have you ever had diarrhea?	1	2	3	4
40	18. Do you ever feel tired?	1	2	3	4
41	19. Does pain interfere with your daily activities?	1	2	3	4
42	20. Do you have difficulty concentrating on things, such as reading the	1	2	3	4
43	newspaper or watching TV?				
44 45	21 Do you ever feel pervoue?	1	2	3	4
46	22. Do you over feel werried?	1	2	2	т 1
47		1	2	3	4
48	23. Do you ever teel easily irritated?	1	2	3	4
49	24. Do you ever feel depressed?	1	2	3	4
51	25. Do you ever have trouble remembering things?	1	2	3	4
52	26. Has your medical condition or treatment process interfered with your family	1	2	3	4
53	life?				
54	27. Has your medical condition or treatment interfered with your social	1	2	3	4
55 56	activities?				
57	28. Has your medical condition or treatment process caused you financial	1	2	3	4
58	difficulties?				
59	For the following questions, the numbers 1-7 represent a scale from "very poor" to "	very g	ood".		
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29. How v	would you rate you	ar overall health in	the past week?			
1	2	3	4	5	6	7
very poor	" to					very good
30. How y	would you rate the	overall quality of	your life in the pas	t week?		
1	2	3	4	5	6	7
very poor	" to					very good

Patients sometimes have the following clinical symptoms. Please indicate the extent of these clinical symptoms or problems you have had in the past week, circling the answer that best applies to you.

	No	A little	Some	Very much
31. Do you cough a lot?	1	2	3	4
32. Do you cough up blood (blood in sputum)?	1	2	3	4
33. Do you feel short of breath when you rest?	1	2	3	4
34. Do you feel short of breath when you take a walk?	1	2	3	4
35. Do you feel short of breath when climbing stairs?	1	2	3	4
36. Have you ever had pain in your mouth or tongue?	1	2	3	4
37. Have you ever had difficulty swallowing?	1	2	3	4
38. Have you ever had tingling/numbness in your hands and feet?	1	2	3	4
39. Have you ever had hair loss?	1	2	3	4
40. Have you ever had chest pains?	1	2	3	4
41. Have you ever had pain in your arms or shoulders?	1	2	3	4
42. Have you ever had any pain in other parts of your body?	1	2	3	4
If yes, please write down the area:				
43. Have you ever taken any painkillers?				
1.Yes 2.No				
If you have used it, does it help much with pain?	1	2	3	4

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In the past 1 week	No	A little	More	А
1. Do you have dry mouth?	1	2	3	4
2. Do your food and drinks taste different than usual?	1	2	3	4
3. Do your eyes hurt, feel uncomfortable, or tear up?	1	2	3	4
4. Do you have hair loss?	1	2	3	4
5. If you have hair loss, does it bother you?	1	2	3	4
6. Do you feel sick or uncomfortable?	1	2	3	4
7. Is your face red and hot?	1	2	3	4
8. Do you have a headache?	1	2	3	4
9. Do you feel less physically attractive due to illness or treatment?	1	2	3	4
10. Do you feel less attractive as a woman due to illness or treatment?	1	2	3	4
11. Do you have difficulty looking at your naked body?	1	2	3	4
12. Are you dissatisfied with your body?	1	2	3	4
13. Are you worried about your future health?	1	2	3	4
In the past 4 week				
14. How interested are you in sex?	1	2	3	4
15. How active are you sexually (do you have sex often)? (With or without sex?)	1	2	3	4
16. If you have sex, to what extent does it bring you pleasure?	1	2	3	4
In the past 1 week				
17. Do you have pain in your arm or shoulder?				
18. Is your arm or hand swollen?				
19. Do you have difficulty lifting or moving your arm to the side?				
20. Do you have pain in the area of your affected breast?				
21. Is the area of your affected breast swollen?				
22. Do you have hypersensitivity in the affected breast area?				
23.Do you have skin problems (e.g. itching, dryness, flaking) in the				
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Supplementary 4. Evalu excerpt, normal commo	ation criteria for common adverse n adverse event evaluation criteri	e events (CTCAE Version 4.0 a is grade 0)	03)	3-078049 on 30 Jr t, including for us	
Auverse Events	1	2	Grading	ses r	5
Hemoglobin g/I	Normal value -10.0	10 0-8 0	8 0-6 5	<u> </u>	5
Leukocytes $(10^9/L)$	Normal value-3 0	3. 0-2. 0	2.0-1.0		
Neutrophils(10 ⁹ /L)	Normal value-1.5	1.5-1.0	1. 0-0. 5		
P(1000000000000000000000000000000000000	Normal value-75	75-50	50-25		
Transaminase ALT/AST	≤2.5×N	2.6-5.0×N	5.1-20×N	>20 ≱data >20 ≱data	
Alkaline phosphatase	$\leq 2.5 \times N$	2.6-5.0×N	5.1-20×N		
Bilirubin	ULN-1.5×N	1. 5-3. 0×N	3.0-10×N		
Creatinine Cr	ULN-1.5 \times N	1.5-3.0×N	3.0−10×N		
Weight gain/loss	5.0-10%	10-20%	≥20%	aini	
Vomiting	Vomiting 1 time in 24h during treatment	Vomiting 2-5 times in 24h during treatment	Vomiting ≥ 6 times in 24h during treatment or requiring fluids	Life-t requir surgent treatment	Death
Coughing sputum	Occasional/mild coughing of sputum	Moderate cough and sputum; interferes with instrumental daily life	Persistent heavy coughing and limited personal self- care	n June 14, ; nilar techno	
Pneumonia	Asymptomatic; clinical examination or diagnostic findings only; no intervention required	Symptomatic (mild cough and/or dyspnea, with or without fever); requires clinical intervention; interferes with instrumental daily	Severe symptoms; limited personal autonomy; need for oxygen	Life-tareatoning respiratoryallysfunction; requiring agent treatment acheotomy or intubatian)	Death

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Acute coronary		Symptomatic,	Symptomatic, unstable	Symptomatic, unstable	Death
syndrome		progressive angina;	angina with/ or acute	anginar with or acute	
		normal cardiac enzymes;	myocardial infarction,	myocardea Sunfarction,	
		hemodynamically stable	abnormal cardiac enzymatic	abnoriana da cardiac	
			parameters,	enzymate garameters,	
	· · · · ·		hemodynamically stable	hemo kan hemo	
Left ventricular			Symptoms of decreased	Uncomer ollable heart	Death
systolic insufficiency	7		ejection fraction	failure	
				ejection	
				requir	
				intervention	
Heart Failure	Asymptomatic, with	Mild to moderate	Symptoms occur at rest or	Life-theatening; requires	Death
	abnormalities detected by	symptoms with activity	with light activity or	urgentereatment (e.g.	
	laboratory tests (e.g.,	or exercise	exercise; requires treatment	contingous infusion	
	natriuretic peptide) or cardiac			therapy or nechanically	
	imaging			assisted circulation)	
Limb edema	Comparison using the greatest	Comparison using the	>30% volume variation	mila L	
	difference in volume or	largest difference in	between limbs; severe	une ar te	
	circumference, with 5% to	volume or	changes in limb shape;	°chr	
	10% variation between limbs;	circumference, 10%	limited personal autonomy	, 20)	
	edema or blurred anatomy that	<~30% difference		25 a gies	
	can only be detected on close	between limbs:		s. It Ag	
	examination	disappearance of skin			
		folds: apparent loss of		Ce E	
		limb anatomy change in		3ibli	
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		shape; interferes with instrumental daily living		149 on 30	
Neurotoxicity - Sensory	Mild sensory abnormalities (including paresthesia), absence of deep tendon reflexes	Moderate objective sensory deficit or sensory abnormalities (including tingling)	Severe objective sensory loss or sensory abnormalities that affect daily life	Persistent in the second secon	Death
Neurotoxicity-motor	Self-perceived weakness with no objective findings	Moderate self-conscious weakness; no significant functional impairment	Self-perceived weakness with functional impairment	o text Paralyxt and da da	Death
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Supplementary 5. Scoring criteria for late radiation injury (RTOG/EORTC 1995) Organ Tissue Mild atrophy, hyperpresentation, partial hair loss Lamellar atrophy, moderate capillary Signific method partial hair loss Ulcers 12 Subcutaneous tissue No change Mild selerosis (fibrosis) Moderate fibrosis but selerosis fibrosis but adipose tissue Severe segrets and loss of subcutaneous adipose tissue Necrosis Necrosis 13 Subcutaneous tissue No change Asymptomatic or mildly symptomatic or firadiated field <10% of the side irradiated field <10
Supplementary 5. Scoring criteria for late radiation injury (RTOG/EORTC 1995) Organ Tissue Crading Sector 7 0 1 2 3 5 5 9 Skin No change Mild atrophy, hyperpigmentation, partial hair loss Lamellar atrophy, dilatation, total hair loss Significand the phy, marked de atropy Ulcers 12 Subcutaneous tissue No change Mild sclerosis (fibrosis) and loss of subcutaneous adipose tissue Mo change Mild sclerosis (fibrosis) and loss of subcutaneous adipose tissue Severe seft for subcutaneous tissue Necrosis 16 Image: Simple
Organ Tissue Organ Tissue Grading Grad
Instance Organ Floor O 1 2 3 5 4 8 Skin No change Mild atrophy, hyperpigmentation, partial hair loss Lamellar atrophy, moderate capillary dilatation, total hair loss Significate depth by, marked depthy, marked depth by, marked depthy, marked depth by, ma
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13 Subclaneous issue No change No change Asymptomatic, nindsy Noderate notions out adipose tissue asymptomatic, slight constriction of irradiated field <10% of the side length of subcuments issue. Constriction of irradiated irradiated field >10% 19 Lungs No change Asymptomatic or mildly symptomatic (dry cough), mild imaging signs Moderate symptomatic pulmonary fibrosis or pneumonia (severe cough), hypothermia, patchy imaging Severe symptomatic pulmonary fibrosis, or insufficiency requiring severe respiratory insufficiency requiring 26 Heart No change Asymptomatic or mildly symptomatic; temporary insufficiency requiring Moderate exertional mild imaging signs Severe anging pectoris; pericardiat effusion; pericardiat tamponade; severe heart failure; 27 Heart No change Asymptomatic or mildly symptomatic; temporary T-wave inversion and ST of anges; sinus Moderate exertional angina; mild pericardiits; Severe anging pectoris; pericardiat effusion; pericardiat tamponade; severe constrictive pericardiits;
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23cough), hypothermia, patchy imagingimaging magingor assisted ventilation2425imagingimaging patchy imagingor assisted ventilation26HeartNo changeAsymptomatic or mildly symptomatic; temporary T-wave inversion and ST changes; sinusModerate exertional angina; mild pericarditis; normal heart size;Severe auging pericardified effusion; severe heart failure;287T-wave inversion and ST changes; sinusnormal heart size; peristent T-waveconstrictive pericarditis; pericardified effusion;3011111271111128111113011111301111130111113011111301111130111113011111301111130111113011111301111130111113011111301111130111113011
25patchy imaging2626HeartNo changeAsymptomatic or mildly symptomatic; temporaryModerate exertional angina; mild pericarditis;Severe anging pectoris; pericard al effusion;pericardial tamponade;27symptomatic; temporary 28angina; mild pericarditis; pericard al effusion;severe heart failure; severe constrictive29
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Supplementary 6. Harris Cosmetic Grade Rating of Cosmetic Breast Preservation/Reconstructive
Surgery Results

Level	Double breast	Double	Breast shape on the affected side	Skin
	symmetry	nipple		
		level gap		
Excellent,	Symmetries	≤2cm	No significant difference with the healthy	Normal
Good			side, normal appearance, no deformation of	
			the breast lift due to scarring, no difference	
			between the affected side and the healthy	
			side in feel	
General	Symmetries	2cm-	The shape of the affected breast is basically	Lightened
		3cm	normal or slightly smaller than the healthy	or shiny
			side, and the feel of the affected side is	color
			slightly worse.	
Bad	Obvious	>3cm	The appearance of the affected side of the	Thick,
	asymmetry		breast changes and is significantly smaller	rubber-
			than the healthy side, and feels poorly in the	like,
			hand	rough

2	Supplementary 7. Baker's cla	assification of the prosthetic envelope
4 5	Grading	Breast Implants
6	I (no accessible envelope)	Breast implants feel as soft as non-operated breasts
7	II(Lightly hardened)	The softness of the breast is slightly worse, the implant can be touched
9		but not seen
10	III(Heavy hardening)	Harder breasts, implants can be easily touched out or visible
11		deformation of the implant
12	IV(severe contracture)	Breasts are hard, painful when touched, skin temperature becomes
14		cold, deformation is obvious
15	Only Baker grade III and IV	are defined as periosteal contracture and require reoperation
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Supplementary 8. Radiotherapy-related adverse reactions and their treatment

1 Radiation-induced skin damage

Early skin reactions are those that occur within three months after the start of radiotherapy and are the most common complications in breast radiotherapy. Approximately 92% of patients receiving postlumpectomy radiotherapy will experience acute radiation-induced skin reactions, mostly grade 1 or 2 mild reactions, with a wet desquamation incidence rate of about 3%. Patients undergoing mastectomy will almost always experience acute radiation-induced skin reactions, mostly grade 2 reactions, with a wet desquamation incidence skin reactions, mostly grade 2 reactions, with a wet desquamation incidence rate of about 10-20%.

Prevention is the main approach to managing radiation-induced skin complications. For grade 1 and 2 injuries, conservative treatment is primarily used. Patients should wear loose, cotton open-front underwear, avoid friction and pressure on the skin in the irradiation area, avoid using irritating products such as soap and shower gel, avoid bathing with hot water or showering the irradiation area, and not apply chemical ointments or adhesive tape. If the skin is red, swollen, itchy, or painful, do not scratch it or apply medication randomly. Follow the doctor's advice for medication, such as triethanolamine cream, compound vitamin B12 solution, and medical radiation protectants. Wet dermatitis can be treated with exposure therapy, keeping the area dry and avoiding secondary infections. Wet dermatitis that does not heal after more than two months may develop into skin necrosis, often requiring surgical treatment, with skin grafting for larger areas.

Late skin reactions include local hyperpigmentation, telangiectasia, atrophy, and fibrosis. For chronic radiation dermatitis with recurrent ulceration and significant worsening, surgery is often used to prevent malignant transformation.

2 Pharyngeal and esophageal reactions

Irradiation of the supraclavicular area can cause pharyngeal pain and difficulty swallowing, which are generally mild and self-limiting. Prevention methods include using new radiotherapy techniques, accurate positioning, precise delineation of the target area, rational design of radiation fields, and reducing or avoiding irradiation of organs at risk. Symptomatic support treatment is provided for severe reactions.

3 Radiation-induced lung injury

Radiation-induced lung injury includes early radiation pneumonitis occurring within 3 months after radiotherapy and late radiation-induced pulmonary fibrosis occurring after 3 months. Approximately 2/3 of patients will develop asymptomatic radiation pneumonitis, which does not require treatment. The incidence of symptomatic radiation pneumonitis is between 1% and 5%, usually occurring within 2 months after radiotherapy or within 6 months after radiotherapy. Patients have symptoms and signs of pneumonia, which can manifest as cough, sputum, or fever, and in severe cases, dyspnea and hypoxia. In particular, when imaging examinations (chest X-rays and CT scans) show inflammatory exudative changes in the lung tissue within the irradiation field, symptomatic radiation pneumonitis can be diagnosed after excluding lung metastasis and tuberculosis. Supportive treatment, including hormones, oxygen therapy, and even mechanical ventilation, can provide complete relief, but some patients may still develop pulmonary fibrosis within 6-12 months, even with treatment. Pulmonary fibrosis is a late injury caused by damage to the lung interstitium and pleura, and in severe cases, it can be life-threatening.

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There is currently no specific treatment for radiation pneumonitis, so prevention is more important than treatment. For patients undergoing whole-breast irradiation alone, it is recommended to use a dose-volume constraint of V20 < 22% for the ipsilateral lung. For those receiving irradiation of the supraclavicular lymph node region, a dose-volume constraint of V20 < 34% and V30 < 22% should be used for the ipsilateral lung to further evaluate the overall radiotherapy plan.

4 Radiation-induced heart damage

Radiation-induced heart disease (RIHD) initially manifests as acute pericarditis and later as coronary artery disease, chronic pericarditis, myocardial fibrosis, cardiomyopathy, heart valve damage, and cardiac conduction abnormalities. A 2013 New England Journal article reported that for every 1 Gy increase in the average dose to the heart, the incidence of major coronary events increased by 7.4%. Reducing the risk of RIHD is also focused on prevention. The most fundamental measure is to minimize or avoid radiation exposure to the heart during radiotherapy. The Chinese Anti-Cancer Association Breast Cancer Diagnosis and Treatment Guidelines and Standards (2015 Edition) recommend that the average radiation dose to the heart should be assessed to be at least below 8 Gy. It is recommended to limit the heart's V30 to less than 10%. In addition, for high-risk populations of RIHD or those with cardiovascular disease, drugs that have a protective effect on the cardiovascular system should be used as soon as

possible. Regular cardiac ultrasound follow-ups should be conducted during the follow-up phase.

5 Upper limb edema

Edema in the affected upper limb is one of the common complications after breast cancer surgery and/or radiotherapy, and the extent of surgery is an important influencing factor. AMAROS research reported that the 1-year, 3-year, and 5-year lymphedema incidence rates for the ALND group were 28%, 23%, and 23%, respectively, significantly higher than the 15%, 14%, and 11% for the SLNB + axillary radiotherapy group. The incidence of upper limb lymphedema after axillary lymph node biopsy alone is 5%. Edema caused by radiotherapy usually occurs 1 to 2 months after the end of radiotherapy. Depending on the time of onset, upper limb edema caused by tumor recurrence in the axilla and supraclavicular region is not considered a true post-treatment complication.

The main prevention method for upper limb edema is to reduce axillary dissection, and postoperative progressive functional exercise is the key to preventing upper limb edema. When upper limb edema occurs, manual massage or compression therapy can be used.

6 Brachial plexus nerve injury

Radiation-induced brachial plexus nerve injury is a rare late complication after breast cancer radiotherapy, with an incidence rate of 1%-4%. Early symptoms include sensory and motor disorders in the affected limb and pain, often accompanied by severe nocturnal pain. Some cases may also have lymphedema, with progressively worsening functional impairment. In the late stage, this can lead to the loss of function of the entire limb, causing lifelong disability for the patient and severely affecting the patient's daily life and rest, with a significant impact on their mental health and quality of life. A preliminary diagnosis can be made based on the patient's radiotherapy history, asymptomatic intervals, and clinical features in clinical practice. However, it is necessary to rule out brachial plexus nerve injury caused by tumor metastasis or compression.

Radiation-induced brachial plexus nerve injury is irreversible, and there is currently no ideal treatment

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method, so prevention is crucial. It is essential to strictly follow the indications for radiotherapy in the lymphatic drainage area and pay attention to the radiotherapy range and radiation dose. For cases without severe pain, active measures should be taken to improve the blood supply of the nerves and surrounding soft tissues, and the earlier the diagnosis and treatment, the better the results. For advanced cases, treatment is aimed at relieving pain and improving quality of life.

7 Second primary tumors

Second primary tumors that can occur after breast cancer treatment include contralateral breast cancer and other malignant tumors such as lung cancer and soft tissue sarcomas. If these second primary tumors can be diagnosed and treated early, they do not affect the patient's survival. Therefore, regular follow-up of patients should be strengthened in clinical practice.

8 Rib fractures

The incidence is less than 1%. In most cases, patients have no noticeable symptoms, and fractures are discovered during bone scans or X-ray examinations. A small number of patients may experience chest wall or rib pain, which generally heals on its own without the need for special treatment.

9 Other side effects

During radiotherapy, patients may experience mild loss of appetite and fatigue. Therefore, it is important to adjust the diet reasonably, advocating for a "high protein, high vitamin, low fat" diet to maintain a balanced nutrition. Regularly review routine blood tests, and if a decrease in white blood cells is found, there is a risk of infection. In such cases, it may be necessary to temporarily pause radiotherapy and follow the doctor's advice for symptomatic supportive treatment.

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Supplementary 9. Radiation Target Volume Naming and Delineation

I. Purpose:

To ensure the smooth conduct of the clinical trial and to guarantee the quality of the clinical

trial.

II. Scope:

This clinical trial.

III. Procedures:

- General Principles of Target Delineation: To be performed on plain CT scans.
- □、 RNI + WBI (BCS)/CWI (Mastectomy)

Standards	2.1 Whole Breast Target CTV_2
Superior	Upper edge of the palpable/CT-visible gland.
Boundary	
Inferior	Lower edge of the palpable/CT-visible gland.
Anterior	5 mm beneath the skin; for small and thin breasts, adjust the anterior boundary to
	0.3 cm beneath the skin or even closer.
Posterior	1-2 mm behind the surface of the pectoralis major fascia (adjacent to the
	retromammary space), leaving no fat gap, including the lymph nodes between the
	pectoralis major and minor muscles and unsampled axillary levels I and II,
	excluding ribs/intercostal muscles.
Medial	Parasternum, at least to the medial edge of the internal mammary vessels.
Lateral	Lateral edge of the palpable/CT-visible gland, anterior to the thoracodorsal artery,
	and anterior edge of the latissimus dorsi muscle.

Standards	2.2Tumor Bed and CTV_1
Tumor	The boundaries of the tumor bed are determined by: The positions of the surgical
Bed	clips; it is recommended to place clips at five points: left, right, superior, inferior,
	and posterior. The extent of seroma, ensuring that any seroma within the gland and
	beneath the scar is included.
CTV_1	Includes the breast glandular tissue and soft tissue extending 10-15 mm beyond the
	surgical tumor bed. For patients who underwent segmental resection, a smaller
	margin of around 10 mm is recommended. If there is no glandular tissue beyond the
	tumor bed, the margin can be appropriately reduced. For patients with positive
	margins, extensive intraductal component (EIC), or severe atypical ductal
	hyperplasia (ADH), the margin must be appropriately expanded.

Standards	2.3 Integrated Target Volume CTV_2 for Whole Breast and Low/Mid Axillary		
	Regions		
Whole	Refer to the Whole Breast Target CTV_2		
Breast			
	Axillary Level I: Anatomic	ally marked by the lateral ed	ge of the pectoralis minor.
Axilla	Axillary Level I	Axillary Level II	Rotter's Lymph Nodes
Superior	Where the axillary	Where the axillary	Includes the superior side
	vessels cross the lateral	vessels cross the medial	of the axillary artery and
	edge of the pectoralis	edge of the pectoralis	5 mm above the axillary
	minor	minor	vein
Inferior	Where the pectoralis	Where the axillary	Inferior boundary of
	major inserts into the ribs	vessels cross the lateral	Axillary Level II
		edge of the pectoralis	
		minor	
Anterior	Anterior surface of the	Anterior surface of the	Posterior surface of the
	pectoralis major and	pectoralis minor	pectoralis major
	latissimus dorsi		
Posterior	Anterior surface of the	Ribs and intercostal	Anterior surface of the
	subscapularis muscle	muscles	pectoralis minor
Medial	Lateral edge of the	Medial edge of the	Medial edge of the
	pectoralis minor	pectoralis minor	pectoralis minor
Lateral	Medial surface of the	Lateral edge of the	Lateral edge of the
	latissimus dorsi	pectoralis minor	pectoralis minor
			5

Standards	Chest Wall Target CTV_CW	
Superior	Superior Clinical markers/subclavian head 0.5-1 cm	
Inferior Clinical markers/inferior edge of the contralateral breast fold		
Anterior Skin, excluding the wire		
Posterior	Ribs and intercostal muscles	
Medial Clinical markers/junction of the sternum and ribs		
Lateral Clinical markers/thoracodorsal vessels and the anterior edge of the latissim		
	muscle	
Note:		
1. The entire scar should be included, and the target area should not be reduced within 2 cm		
above a	above and below the scar.	
2. Postoperative changes visible on CT (such as granulomas, fibrosis, and spiculated muscle		

irritation signs) should be included.

Standards	2.5 Supraclavicular and Infraclavicular Lymph Node Area CTV_LN
Superior	Inferior edge of the cricoid cartilage
	0.5-1 cm below the clavicular head, at the level where the brachiocephalic vein
Inferior	disappears, merging with the whole breast/chest wall target area
	Superior part: posterior surface of the sternocleidomastoid muscle; Inferior part:
Anterior	posterior surface of the pectoralis major muscle
	Superior part: posterior edge of the anterior scalene muscle; Inferior part: anterior
Posterior	edge of the ribs and intercostal muscles
	Superior part: internal jugular vein, covering the interscalene triangle to the level of
	the transverse cervical artery and vein; Inferior part: junction of the subclavian vein
Medial	and internal jugular vein
	Superior part: lateral edge of the sternocleidomastoid muscle; Inferior part: lateral
Lateral	edge of the pectoralis minor muscle
Note:	
1. Avoid t	he surgically treated axillary area (Level I and part of Level II).
2. Include	the non-surgically treated area of axillary Level II.

Standards	2.6 Internal Mammary Lymph Node Area CTV_IMN
	Injection into the internal area of the clavicle; for high-risk patients, extend to the
	junction of the internal jugular vein, subclavian vein, or brachiocephalic vein, and
Superior	the internal mammary vein
Inferior	Upper edge of the fourth rib cartilage
	Posterior surface of the pectoralis major muscle and the posterior surface of the
Anterior	sternum
Posterior	Pleura or 5 mm behind the posterior aspect of the internal mammary vessels
	5 mm inside the internal mammary vessels, covering the space between the sternum
Medial	and the vessels
	5 mm outside the internal mammary vessels, to the outer edge of the
Lateral	brachiocephalic vein
Note:	
1. For hig	h-risk patients, the superior boundary extends to the junction of the internal jugular
vein, sı	abclavian vein, or brachiocephalic vein, and the internal mammary vein.
2. It is rec	commended to extend the coverage in the medial and lateral directions (at least) by 5
mm.	

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Standards	2.7 Intraclavicular Lymph Node CTV_intraclavicular-LN
Superior	Level of the transverse cervical artery
Inferior	Upper edge of the brachiocephalic trunk
Medial	Midline of the body
Lateral	Inner boundary of the upper clavicle region
Note:	
1. When i	rradiating the internal mammary lymph nodes, routine delineation is recommended.
2. When t	here is capsular invasion of the lymph nodes in the axillary Level II/III region,
routine	delineation is recommended.
2 Detiont	a with primary types investor of the deep face or types located medially and

Patients with primary tumor invasion of the deep fascia or tumors located medially and 3. superiorly within the breast may be considered for delineation.

 Ξ , Omission of RNI, WBI (BCS) only, no CWI (total mastectomy)

Standard	3.1 Whole Breast Target CTV_2
Superior	Upper edge of palpable/CT-visible gland.
Inferior	Lower edge of palpable/CT-visible gland.
	Subcutaneous tissue 5 mm beneath the skin; for thin/small breasts, adjust anterior
Anterior	boundary to 0.3 cm beneath the skin or even closer.
	1-2 mm behind the surface of the pectoralis major fascia (adjacent to the
	retromammary space), leaving no fat gap, excluding lymph nodes between
	pectoralis major and minor muscles and unsampled axillary levels I and II,
Posterior	excluding ribs/intercostal muscles.
Medial	Parasternal, at least to the medial edge of the internal mammary vessels.
	Lateral edge of palpable/CT-visible gland, anterior to the thoracodorsal artery, and
Lateral	anterior edge of the latissimus dorsi muscle.

Standard	3.2 Tumor Bed and CTV_1
Refer to Sta	andard 2.2 Tumor Bed and CTV_1

Standard 3.3 Integrated Target Volume CTV_2 for Whole Breast and Low/Mid Axillary

Refer to Standard 2.3 Tumor Bed and CTV_1

Supplementary 10. Prescribed Radiation Dose and Evaluation

I. Purpose: To ensure the smooth conduct of the clinical trial and to guarantee the quality of the clinical trial.

II. Scope: This clinical trial.

III. Procedures:

1. Prescribed Dose and Fractionation:

1.1. RNI + WBI (BCS)/CWI (mastectomy): 5000 cGy in 25 fractions, 200 cGy per day, five days a week. For breast-conserving patients, a boost to the tumor bed is required, sequentially administered after whole-breast irradiation, with a dose of 1000 cGy-1600 cGy in 5-8 fractions, 200 cGy per day. Alternatively, a hypofractionated radiotherapy scheme can be chosen, with a radiation dose of 4000-4256 cGy in 15 to 16 fractions. For breast-conserving patients, a sequential tumor bed boost is performed after completion of whole breast irradiation, as determined by individual center investigators. It can be delivered using conventional fractionation, with a dose of 1000 cGy in 5 fractions at a rate of 200 cGy per day, or by using hypofractionation, with a dose of 798 cGy-1064 cGy in 3 to 4 fractions at a rate of 266 cGy per day. If there are high-risk factors for local recurrence, such as positive surgical margins, close margins, or young age, the radiation dose for the tumor bed boost may be increased to 1400-1600 cGy in 7 to 8 fractions at a rate of 200 cGy per day.

1.2. RNI omitted, only WBI (BCS), no CWI (mastectomy): 4000 cGy in 15 fractions or 4250 cGy in 16 fractions, 266 cGy per day (hypofractionation), five days a week; or 5000 cGy in 25 fractions, 200 cGy per day (conventional fractionation), five days a week. A boost to the tumor bed is required, sequentially administered after whole-breast irradiation, with a dose of 1000 cGy-1600 cGy in 5-8 fractions, 200 cGy per day.

2. Dose Distribution and Organs at Risk Limits:

2.1. The prescribed dose should cover at least 95% of the PTV in 95% of the target area, with specific dose distribution determined by each center's policy. 2.2. Organs at risk limits should refer to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) standards.

2.3. For patients with left breast cancer, RNI + WBI (for BCS) / CWI (for mastectomy)

should have a mean heart dose (Dmean) ≤ 8 Gy, while WBI (for BCS) alone should be limited to a Dmean ≤ 5 Gy.

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Supplementary II Dose distribution and organ choangerment mints		
Target Volume	Dmax	Dmi
Whole Breast PTV 2	≤107%	≥90%
Tumor Bed PTV 1	<107%	>90%
Whole Breast and Low-to-Mid Axilla Integrated Target Volume PTV 2	<107%	>90%
Chest Wall PTV CW	<110%	>909
Supraclavicular (±intranodal clavicular) PTV LN	<110%	>909
Internal Mammary PTV IMN	<110%	>809

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Organs	Volume	Type of	Observation	Dose (Gy)	Incidence	Dose volume
		irradiation	index	or dose	(%)	parameter
		(partial		volume		description
		organ or		parameter		
		specially				
		indicated)				
Spinal	Partial	3DCRT	Spinal cord	Dmax=50	0.02	Includes all
Cord	spinal cord		lesions			spinal cord
	Thoracic					cross-sections
	medulla					
Pharynx	pharyngeal	3DCRT	Dysphagia	Dmean<	$<\!\!20$	
	constrictor	6	and	50		
	muscle		shortness of			
			breath			
larynx	Total larynx	3DCRT	Edema	Dmean<	$<\!\!20$	No
				44		chemotherapy,
	Total larynx	3DCRT	Edema	V50<27%	$<\!\!20$	based on a
						single study of
						patients
						without
						laryngeal
						cancer
lung	whole lung	3DCRT	Pneumonia	V20≤30%	<20	Double lung.
	whole lung	3DCRT	Pneumonia	Dmean=7	5	Slow dose
	whole lung	3DCRT	Pneumonia	Dmean=13	10	response
	whole lung	3DCRT	Pneumonia	Dmean=20	20	Without whole
	whole lung	3DCRT	Pneumonia	Dmean=24	30	lung treatment
	whole lung	3DCRT	Pneumonia	Dmean=27	40	irradiation
Esophagus	Whole	3DCRT	≥3 Grade	Dmean<	5-20	Contains
	Esophagus		acute	34		various dose
			esophagitis			limiting
	Whole	3DCRT	\geq grade 2	V35<50%	<30	factors. Seems
	Esophagus		acute			to be related to
			esophagitis			dose volume
	Whole	3DCRT	\geq grade 2	V50<40%	<30	
	Esophagus		acute			
			esophagitis			
heart	Pericardium	3DCRT	pericarditis	Dmean<	<15	Based on
				26		individual
	Pericardium	3DCRT	pericarditis	V30<46%	<15	studies
	Whole heart	3DCRT	distant	V25<46%	<1	High
			cardiac			standards for

Supplementary 12. Organ dose/volume/impact data for routine split exposures (except where noted): QUANTEC

			death			assessing
						security based
						on predictive
						models
Liver	Whole	3DCRT	Typical	Dmean<	<5	Exclude
	Liver - GTV		RILD	30-32		patients with
						existing liver
						disease or
						liver cancer
	Whole	3DCRT	Typical	Dmean<	<50	Patients with
	Liver - GTV		RILD	42		liver disease
	Whole	3DCRT	Typical	Dmean<	<5	or
	Liver - GTV		RILD	28		hepatocellular
	Whole	3DCRT	Typical	Dmean<	<50	carcinoma
	Liver - GTV		RILD	36		with a Child-
						Pugh rating of
						A, but not
						active
						hepatitis B,
						were included
						as observation
						indicators
	Whole	3DCRT	Ulcer	D100<45	<7	
	stomach			•		

QUANTEC: Quantitative Analysis of Illumination Response in Clinically Normal Tissues; 3DCRT: Three-Dimensional Conformal Radiotherapy; GTV: Gross Tumor Volume; RILD: Radioactive Liver Injury; RTOG: Radiation Therapy Oncology Group of Amer

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Frozen/paraffin tissue	×					72										
Pathology	×*						h					ng,				
Tumor markers	×					×	×	×	×	×	×		×	×	×	×
Breast + LN ultrasound/MR	×					×	×	×	×	×	×	en.bm × raining	×	×	×	
Mammography	×*						×		×		×	, j <mark>i co</mark> , an	×		×	-
Chest X-ray/CT	×					×	×	×	×	×	×		×	×	×	×
Abdominal ultrasound/CT	×					×	×	×	×	×	×	on June ×une	×	×	×	×
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Physical examination	×	×	×	×	×	×	x	×	×	×	×	×ioc	×	×	×	1

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ECOG score	×				×		×		×		×)24. gnei elate	×		×	
Blood count	×**	×	×	×	×	×	×	×	×	×	×		×	×	×	
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Supplementary 14. Data Management

1. Source Data Recording

Monitoring personnel will verify source data to confirm that the data entered by authorized personnel at the trial center into the electronic Case Report Form (eCRF), i.e., the source data, is correct, complete, and indeed originated from the source documents.

Source documents (paper or electronic) refer to patient data recorded at the earliest time and include but are not limited to: hospital records, laboratory records, memos, patient-reported outcomes, assessment checklists, data recorded on automated instruments, microfiche, photographic films, Xrays, etc.

Source documents requiring verification of data integrity and validity must not be altered or destroyed and must be retained in accordance with the applicable regulatory retention policies.

For source data verification, investigators and trial institutions must provide monitoring personnel with direct access to relevant source documents and reports for audit purposes and Institutional Ethics Board/Ethics Committee (IEB/EC) review. Trial centers must also allow regulatory authorities to conduct inspections.

2. Use of Computer Systems

When clinical observation results are entered directly into the computerized medical record system of the study center, electronic records may be considered as source documents if the system has been validated according to regulatory requirements for computerized systems adopted in clinical research. Original data should be saved using appropriate computerized data collection systems. If original data requires modification, the system must retain visual inspection audit trails showing the original data and reasons for modification, along with the names and dates of modification.

3. Case Report Forms

This study utilizes electronic Case Report Forms (e-CRFs) for data collection, completed using the Electronic Data Capture (EDC) system specified by the principal investigator. The designated vendor appointed by the principal investigator will provide training to trial centers and a suitable e-CRF completion manual to the research centers.

All e-CRFs are completed by designated, trained personnel at the trial center, and the investigator or designated personnel must review, electronically sign, and date the e-CRFs.

4. Data Quality Assurance

The clinical trial office where the principal investigator is located is responsible for data management for this study, including monitoring/audit of data quality. Clinical research data will be collected via eCRFs using the EDC system. Data entry into the ECD system will be the responsibility of the research center. In case of discrepancies, the clinical trial office where the principal investigator is located will request explanations from the research center, and this process will be electronically resolved within the EDC system.

The sponsor will develop an EDC study quality standards document outlining methods for quality checks on the data.

Data from center laboratories will be sent directly to the principal investigator, who will process and electronically transfer these data according to the standard operating procedures recognized by the

principal investigator for center laboratories.

e-CRFs and correction documents will be retained in the EDC system during the auditing process. The data retained by the principal investigator will be systematically backed up according to standard operating procedures recognized by the principal investigator for the vendor, and records of research data retention will be kept.

5. Independent Data Safety Committee

A Data Safety Committee will be established, consisting of an odd number of members (typically 5), who are independent of the project team and have signed confidentiality agreements. The committee will primarily conduct a review analysis of positive results (subject relapse and metastasis) and understand the actual study results (without statistical analysis) when half of the subjects are enrolled, voting on whether adjustments to the study protocol are necessary

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Supplementary 15. Quality Management Plan

1 Quality Control

- 1) Qualifications of Study Personnel: All personnel involved in this trial, including investigators, nurses, statisticians, clinical trial observers, etc., must undergo clinical trial training and work under the guidance of senior professionals.
- 2) Investigators and other personnel involved in the study should fulfill their responsibilities and strictly adhere to the clinical trial protocol, employing standard operating procedures to ensure the implementation of quality control and quality assurance systems.
- 3) All observed results and findings in the clinical trial should be verified, and quality control must be conducted at every stage of data processing to ensure data integrity, accuracy, authenticity, and reliability.
- 4) Investigators and other personnel involved in the study should have sufficient time and reliable sources of subjects for conducting the study.
- 5) All projects involving imaging and laboratory testing should be carried out by units that comply with national standards.
- 6) Specimens requiring collection in this study should be collected by designated individuals, and follow-up data should be collected and stored by designated personnel.
- 7) Testing procedures should be conducted according to the specified Standard Operating Procedures (SOPs).
- 8) When modifications to the study protocol are required, the Ethics Committee should be convened according to SOPs, fully utilizing the Ethics Committee's functions to ensure the protection of subjects' interests.
- 9) Each participating unit should establish a file folder, save all original materials as required in the protocol, and arrange them in chronological order for verification purposes.
- 10) Contract research organizations must appoint trained monitors for the study, who should have relevant medical and pharmaceutical backgrounds, and conduct inspections of the research projects according to SOPs (including: pre-trial visits, initiation visits, routine monitoring visits, and end-of-study visits; see "Monitoring Plan").
- 11) Inspectors should systematically examine clinical trial-related activities and documents to assess whether the trial is conducted in accordance with the protocol, SOPs, and relevant regulatory requirements, and whether trial data are recorded in a timely, truthful, accurate, and complete manner. Inspections should be conducted by personnel not directly involved in the clinical trial.
- 12) The establishment of inspection work is to ensure that clinical trials are conducted in accordance with the requirements of the protocol, SOPs, and relevant regulations. Contents include: a) How is the clinical research operated? b) Is the implementation in line with the requirements of the study protocol? c) Is the principal investigator effectively and appropriately monitoring the progress of the study? d) How is the quality of the study: whether the study personnel, study centers, and data trial centers adhere to the requirements of SOPs? e) Are the data copied onto the Case Report Form (CRF) consistent with the original data? f) Overall trial quality (identifying the root causes of issues). g) Are study documents present? Are they stored systematically? Are they interpretable (can trial data be reconstructed from study documents)? h) Inspection of monitoring reports attempts to identify quality trends and consult on corrective measures for procedural issues that

 have arisen.

13) Regular inspections, preparation of inspection reports, and holding meetings with relevant personnel to discuss issues identified during the inspection.

2 Monitoring Plan

The monitor conducts three types of visits: study initiation visits, routine visits, and close-out visits.

2.1 Study Initiation Visits

Meet with the principal investigator, establish a visit plan, and introduce the monitoring objectives and plans to the investigator. Review includes: training manuals, forms, study protocols, qualifications of participating researchers, and compliance with data management SOPs, etc. If necessary, a start-up meeting can be convened to discuss the protocol and work content with all doctors and other staff participating in the study, clarify each person's responsibilities, explain the SOP requirements for data entry standards, and the preservation of original data.

2.2 Routine Visits

- ① Before each visit, review the progress of the trial and unresolved issues from previous visits, contact the investigator to confirm the visit date, develop a plan and agenda for this visit, prepare the required documents and items for the visit.
- ② Meet with the investigator to explain the main tasks of this visit, understand the progress of the trial (subject enrollment status, CRF completion status, informed consent signing status, etc.), and the resolution of problems identified during previous visits.
- ③ Check and update the investigator's management files, verify the original documents and CRF forms (pay attention to compliance, completeness, consistency with the protocol, discovery, and reporting of SAEs), check trial materials (storage conditions, distribution and recovery records, compliance with protocol requirements).
- ④ Collect CRF forms.
- (5) Record any issues discovered, discuss and resolve the problems identified during this visit with the investigator, exchange progress and experiences with other research units.
- 6 Store items retrieved, signed informed consent forms, CRF forms, etc., as required.
- ⑦ Complete the visit report, update various records, track and resolve any issues discovered, and schedule follow-up visit plans.
- (8) SAEs that occur during the clinical trial must be reported to the Ethics Committee within 24 hours.
- (9) Any changes to the protocol, CRF forms, etc., during the trial require approval from the Ethics Committee. Documents to be submitted to the Ethics Committee during the trial include: protocol amendments, informed consent form amendments, SAE reports, recruitment advertisements (if used).

2.3 Close-Out Visits

- ① Review any outstanding issues from routine visits and confirm their resolution.
- 2 Confirm the visit time, develop a plan and agenda for this visit.
- ③ Confirm the completeness and updating of the investigator's management files.

- ④ Confirm that all CRF forms have been collected.
- 5 Confirm the reporting and tracking of SAEs.
- 6 Check the records of the transport, distribution, and retrieval of various materials for the study.

 \bigcirc Discuss and summarize, confirm any outstanding issues and follow-up work, explain the requirements for the preservation of trial-related documents.

⁽⁸⁾ Follow-up work: Complete the trial close-out monitoring visit report, notify the Ethics Committee of the trial's conclusion, continue to track and resolve any outstanding issues, and archive all documents. Documents to be submitted to the Ethics Committee after the trial ends include: trial closure letter, SAEs after trial closure.

3 Data Requirements

Protocol: After careful reading and agreement, the principal investigator must sign and strictly adhere to the protocol implementation.

Clinical Trial Data: All various original clinical trial data should be recorded promptly, truthfully, accurately, and completely, and copies of laboratory test reports should be retained. The principal investigator must retain records and documents of the study implementation process, including eCRFs, informed consent forms, laboratory test results, and radiotherapy plans, for 5 years after the completion or termination of the study, or for a longer period as required by regulatory authorities (whichever is longer). After this time period, the documents may be destroyed in accordance with local regulatory requirements.

4 Study Summary

Once the required total number of cases is reached and verified, the data analysis center performs data analysis. Based on the statistical analysis report, the responsible unit of the clinical trial and participating units write a summary of the clinical trial and sub-center summary table according to the principles of Good Clinical Practice (GCP) clinical trial guidance.

5 Research Funding

The RecurIndex-related testing expenses for this trial are provided by the collaborating party, with specific funding arrangements outlined in a signed contract.

6 Financial Transparency

The principal investigator is required to provide complete and accurate financial information in accordance with Chinese regulations, in order to submit comprehensive and accurate financial statements or disclosure statements to relevant health authorities. The principal investigator is responsible for providing financial information from the beginning to the completion of the study period.

Supplementary 16. Statistical Analysis

1. Population Analysis

Full Analysis Set (FAS): Efficacy analysis will be conducted for all cases randomized according to the intention-to-treat (ITT) principle, and analyzed based on their randomized groups, regardless of the actual radiation therapy group received.

Per-Protocol Set (PPS): Subjects from the FAS set will be excluded if they have major protocol violations that could potentially affect the primary efficacy endpoint IDFS analysis. Efficacy evaluation for this study will be conducted for both FAS and PPS sets, with FAS serving as the primary analysis set.

Safety Set (SS): All subjects randomized and receiving at least one session of radiation therapy belong to the safety analysis set. This dataset utilizes actual radiation therapy groups and is used for safety analysis.

2. Demographic and Baseline Characteristics

Descriptive statistical analysis will be conducted for demographic characteristics such as age, gender, height, weight, as well as other baseline features including medical history.

3. Participant Distribution

Descriptive statistical analysis will be performed on participant enrollment status, study completion status, premature study withdrawal, etc. A tabular summary will outline the distribution of participants across different analysis populations.

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4. Efficacy Analysis

Efficacy analysis will be based on both FAS and PPS, with FAS serving as the primary analysis set. Primary Endpoint Analysis: Invasive Disease-Free Survival (IDFS) serves as the primary efficacy endpoint of this study, defined as the time from randomization to the earliest occurrence of invasive cancer local recurrence, distant metastasis, or death, whichever comes first. The occurrence of invasive disease recurrence will be determined by the assessment results obtained by an independent review committee using pathological or imaging examinations. Patients who have not experienced invasive cancer local recurrence, distant metastasis, or death will have their last follow-up date considered as the censoring date. Patients who have not undergone imaging follow-up after baseline will have the randomization date considered as the censoring date. Cox proportional-hazards model will be used for the analysis of the primary endpoint to calculate the Hazard Ratio and its 95% confidence interval, adjusting for stratification factors and other covariates. Additionally, a Cox proportional-hazards model without covariates will be used to support the analysis results of the primary endpoint. Furthermore, the median invasive disease-free survival for both groups (Group A vs. Group B) will be calculated using the Kaplan-Meier (KM) method, including the 95% confidence interval. KM plots will be used to illustrate the trend of IDFS over time.

Secondary Endpoint Analysis: The analysis will compute the Annual Failure Rate (AFR) for each group, along with the corresponding 95% Clopper-Pearson confidence interval. Local recurrence-

free survival (LRFS), distant metastasis-free survival (DMFS), relapse-free survival (RFS), overall survival (OS), disease-free survival (DFS), and breast cancer-specific mortality (BCSM) will be analyzed using the KM method to determine the median values (including the 95% confidence interval). Changes in total scores of EORTC QLQ-C30 and EORTC QLQ-BS23 from baseline will also be summarized.

5. Safety Analysis

Safety analysis will be based on the Safety Set (SS).

The safety analysis will include all enrolled patients who have received at least one session of radiation therapy, grouped according to the actual treatment received by the patients.

Safety will be assessed by summarizing adverse events, changes in laboratory test results, vital sign changes, and exposure to study treatment, reported by treatment group.

All adverse events (AEs) will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) Acute Radiation Morbidity Scoring Criteria (1995), and RTOG/EORTC Late Radiation Morbidity Scoring Criteria (1995). All adverse events occurring during treatment (Treatment Emergent Adverse Events, TEAEs, defined as events occurring within 30 days after the end of the last radiation therapy session), TEAEs of Grade 3 or higher, serious adverse events (SAEs), radiation-related SAEs, and TEAEs leading to trial discontinuation will be summarized by system organ class, preferred term, and group in terms of number and percentage. Additionally, the severity and relatedness of TEAEs to radiation therapy will also be summarized by system organ class, preferred term, and group. If a patient experiences the same adverse event multiple times, the maximum reported severity will be used for summarization.

6. Exploratory Studies

Exploratory studies will investigate the relationship between peripheral blood T lymphocyte subsets and the immunomodulatory effects of radiotherapy, as well as the relationship between circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and distant tumor eradication effects.

7. Interim Analysis

Interim analysis is not planned for this trial.

8. Final Analysis

The final analysis for this study is planned to be conducted when the last enrolled patient completes radiotherapy and reaches a follow-up of 5 years.

Supplementary 17. Physical status ECOG scoring criteria	~ .
ECOG scoring criteria	Scoring
Mobility is completely normal and does not differ in any way from that befor	e the 0
onset of the disease	
Can walk freely and perform light physical activities, including general house	ework 1
or office work, but cannot perform heavier physical activities	
Able to walk freely and take care of themselves but have lost the ability to w	ork 2
and can get up and move around at least half of the time during the day	ork, 2
Outer and the ship of the second at least han of the time during the day	1 f
Only partially able to take care of themselves, bedridden or wheelchair bound	1 Ior 3
more than half of the day	
Bedridden and unable to care for themselves	4
Death	5



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description		
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ($pg3$. <i>line 3</i>)		
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (<i>pg4. line 44</i>)		
	2b	All items from the World Health Organization Trial Registration Data Set (Supplemental 14)		
Protocol version	3	Date and version identifier (<i>pg4. line 42</i>)		
Funding	4	Sources and types of financial, material, and other support ($pg14$. line 43)		
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pg3. line 9)		
	5b	Name and contact information for the trial sponsor (pg3. line 54)		
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. (<i>pg14. line 33</i>)		
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)		
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (<i>pg4. line 60</i>)		
	6b	Explanation for choice of comparators ($pg5$. line 20-43)		
Objectives	7	Specific objectives or hypotheses (pg8. line 14)		

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (e superiority, equivalence, noninferiority, exploratory) ($pg4$. line 26)
Methods: Partici	pants,	interventions, and outcomes
Study setting	9	Description of study settings (eg, community clinic, academic hospital and list of countries where data will be collected. Reference to where list of study sites can be obtained ($pg6$. <i>line 59</i>)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibili criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ($pg7$. line 7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication including how and when they will be administered (<i>pg7. line 17 and pg9. line 52</i>)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ($pg10$. line 43)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ($pg7$. <i>line 52</i>)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Not available)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (<i>pg8. line 19</i>)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins an washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Table 3)
Sample size	14	Estimated number of participants needed to achieve study objective and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (<i>pg11. line 41</i>)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ($pg7$. <i>line 52</i>)
Methods: Assign	nment	of interventions (for controlled trials)
Allocation:		

1				
1 2 3 4 5 6 7 8	Sequence generation	16a	Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (<i>pg7. line 41</i>)	
9 10 11 12 13 14	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (<i>pg7. line 45</i>)	
15 16 17	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ($pg7$. <i>line 52</i>)	
18 19 20 21 22	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (Not applicable)	
23 24 25 26		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (Not applicable)	
27 28	Methods: Data collection, management, and analysis			
29 30 31 32 33 34 35 36 37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (<i>pg11. line 20</i>)	
38 39 40 41		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ($pg10$. line 40)	
42 43 44 45 46 47 48	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (<i>pg11. line 22</i>)	
49 50 51 52	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (Supplementary 15)	
53 54 55		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (Supplementary 15)	
56 57 58 59 60		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (Supplementay15)	

Methods: Monitor	ing			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Supplementary 16)		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (Supplementary 15)		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Supplementary 15)		
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Supplementary 16)		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ($pg12$. <i>line 35</i>)		
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (<i>pg12. line 45</i>)		
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)		
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ($pg12$. line 48)		
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ($pg14$. <i>line</i> 51)		
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Supplementary 16)		
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		

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Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (<i>pg4. line 44</i>)
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ("Informed Consent Form for RCT" and "Informed Consent Form for Tumor Tissue Biopsy")
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (Supplementary 17)
	Dissemination policy Appendices Informed consent materials Biological specimens	Dissemination 31a policy 31b 31b 31c Appendices Informed consent 32 Biological 33 specimens 33

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.

Author notes: the above pages and line numbers refer to the first submission synthesized PDF, titled *bmjopen-2023-078049_Proof_hi*.